PERNICIOUS ANAEMIA.

A. C. STRAIN.

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PERNICIOUS ANAEMIA.

Pernicious Anaemia, although no longer regarded as a rarity especially in hospital practice, is nevertheless comparatively seldom met with in general practice, and perhaps less seldom recognised. It was my good fortune while resident at Chalmers Hospital to have several interesting cases of this disease under my observation and I propose to detail and investigate these along with several cases which were in hospital during the previous session. I am indebted to Dr. Gulland for permission to make use of these cases.

Although Pernicious Anaemia had been previously described by various authors in different countries it was not till Addison published his clinical and pathological reports on cases that it came definitely to be looked on as a separate entity quite apart from chlorosis and secondary anaemia. Since then the literature on the subject has been very abundant, yet in spite of the numerous investigations which have been carried out, we are still ignorant in regard to many points and especially in regard to the aetiology of the disease.

AETIOLOGY.

From observation of various statistics Pernici-

ous Anaemia appears to be more prevalent in some parts of the world than in others. Thus, it is said to be fairly prevalent at Zurich - rare in Prague and very rare in New York, but no explanation has ever been offered as to why this should be so.

Sex.- A. F. Müller has collected a large number of statistics and these show that females are more frequently affected than males. Ehrlich[1] has collected notes of 240 cases to test the question of sex. He found that 130 were females and 110 males. Berlin Hospital Reports for 10 years 1887-98 show 172 Females and 102 Males. In American statistics there is a striking contrast, as there male cases are in excess of female cases. Cabot[2] found of 110 cases 57 were males and 53 females while McCrae found 48 males and 14 females out of 62 cases.

Osler[3] states that males are more frequently affected than females and out of 27 cases he had 17 males and 10 females. Of the 14 cases which I have to record 8 of these were males and 6 females.

Age.- Ehrlich[1] has analysed 240 cases and the following table shows his results:-

Years	1 - 10	Cases 1.
	10 - 20	" 22.
	20 - 30	" 61.
	30 - 40	" 67.
	40 - 50	" 47.

Years	50 - 60	Cases	33.
	60 - 70	"	7.
	70 - 80	"	2.

Hutchinson[4] found no case in children at Great Ormonde Street Hospital and he states that a diagnosis of pernicious anaemia in children must be uncertain because of the changes which occur in the blood in insignificant diseases in children. The youngest of my cases was 23 years while the oldest was 68. It may be said that pernicious anaemia is most commonly found between 25 and 50 years of age.

Heredity.- Statistics from all authors would seem to prove that there is no distinct evidence of heredity in regard to this disease. Sinkler and Eshner[5] report 3 cases of pernicious anaemia in one family but their report is incomplete, and in the light of modern means of diagnosis it must be regarded as of no value. In only one of the following cases was there a definite history of heredity. In this case the patient's father died in the Royal Infirmary, Edinburgh, from pernicious anaemia aet 57, and the patient's sister who used to visit him in the ward had also the appearance of it, although she did not complain, and her blood was never examined. There appears to be nothing in the constitution or in the social condition of the patient which specially predisposes to the disease.

Pregnancy and Labour.-

In the earlier literature pregnancy and labour were much oftener regarded as a cause of pernicious anaemia than now. In 1878 Eichhorst published a paper in which 35% of the cases could be traced to pregnancy or labour. In several of these cases there was hyperemesis, severe haemorrhage at labour, or some other cause which might account for a severe anaemia, and it is highly probable that many of his cases were not genuine pernicious anaemias although in others there was no abnormal symptom during the pregnancy with the exception of the spontaneous development of a severe anaemia which proved fatal. Lebert tried to explain the occurrence of pernicious anaemia by some special nervous influence. More recent literature contains very little reference to the association between pernicious anaemia and pregnancy. Ewing[6] states that at Sloane Maternity Hospital from 1892-99 he saw many cases of severe anaemia but none of the progressive pernicious type.

Ahlfeld states that in a wide experience of this disease he has not met a case following pregnancy.

Elder and Matthews[7] report 2 cases of fatal pernicious anaemia following labour. Both were young women aet 29 and 31 respectively and in both,

the disease was of acute type and rapidly proved fatal. They could find no cause for the condition although they state that the teeth were very much decayed. They believe that it is at least reasonable to assume that under exceptional circumstances (not yet understood) toxic products of a haemolytic order may be thrown into the blood after parturition which may either directly set up a pernicious anaemia or seriously aggravate any pre-existing tendency to the disease. Henderson[8] found after a series of counts in hospital patients in Glasgow that the red blood corpuscles and haemoglobin were both slightly reduced. The count after labour he found to depend chiefly on the amount of blood lost but it was never very seriously reduced and regeneration rapidly took place. One case (which is not included in the number) was sent in to hospital as anaemia after labour, and her blood presented many features of pernicious anaemia but when everything was considered it was decided that the case was really one of secondary anaemia.

Repeated Haemorrhages.-

This has also been advanced as a cause of pernicious anaemia. It seems highly probable that many of the cases described under the previous

heading were really due to haemorrhage hence it is not surprising to find that other writers have sought to trace the origin of the disease to haemorrhages occuring elsewhere in the body. Chief amongst the advocates of this theory is Stockmann, who goes the length of urging that all cases of progressive pernicious anaemia are due to repeated haemorrhages, but that theory can scarcely account for the fact that haemorrhage should in one person be followed by a secondary anaemia, while in others it should produce pernicious anaemia. I have not been able to find anywhere in the literature another writer who agrees with Stockmann's views. Gilbert and Garnier[35] found that the necrotic areas in the liver of pernicious anaemia were comparable to the lesions found in animals after severe repeated haemorrhages.

Syphilis.-

In the older writings syphilis was regarded as a fairly common cause of pernicious anaemia but more recently reports have not gone to strengthen the view that syphilis may directly cause pernicious anaemia. Again there is great difficulty in forming any accurate estimation from statistics because of the great prevalence of syphilis, so that the occurence of pernicious anaemia in a syphilitic may be only a coincid-

ence, and not cause and effect. If syphilis were really the cause of pernicious anaemia then one might expect benefit to follow antisyphilic treatment but it is well known that it is not so.

Gastrointestinal disorders.-

The number of cases of pernicious anaemia which present symptoms of gastrointestinal disturbance are so numerous that it seems only natural that many investigators should have attempted to trace the origin of the disease to some lesion in the alimentary tract. The fact also that anaemia so similar to pernicious anaemia can be produced by the Bothriocephalus Latus seems to lend support to the theory of gastrointestinal disturbances being the primary cause of pernicious anaemia.

Whether the gastrointestinal disturbances are the essential cause, or whether they are only symptoms of the disease, from my experience of the following cases I believe that they are so important as to require very definite treatment, and in at least one case I have been able to date the beginning of improvement, both in the blood and in the general condition of the patient to active treatment of the gastrointestinal symptoms. Sandoz[9] makes the somewhat bold claim that he cured a case of pernicious anaemia by

continued washing out of the stomach, while others have reported improvement after free evacuation of the bowels. In not a few recorded cases, which during life were regarded by competent observers as pernicious anaemia, there has been found postmortem a cancerous tumour of some part of the alimentary canal, but in the majority of such cases the anaemia is really a secondary anaemia and the cancer is the primary cause of death. The number of such cases is considerable, and the difficulty of absolute diagnosis is so great, that a very careful examination should always be made for gastric cancer in cases of marked anaemia with gastric symptoms. Israel[10] assumes that the tumour often causes repeated haemorrhages which may be the cause of the anaemia and he reports one case in which postmortem there was a small cancerous tumour and evidences of recent haemorrhages in the neighbourhood of the tumour.

Ehrlich[1] sums up the probable relationship between pernicious anaemia and gastric cancer as follows,

> "In the first place there are cases of gastric carcinoma in which a progressive pernicious anaemia develops on the soil prepared by the severe cachexia and anaemia, and in the second place there are cases of pernicious anaemia in which a favourable soil is created for the development of a carcinoma of the stomach possibly through the medium of the atrophy of the mucous membrane."
>
> In the latter cases the carcinoma usually produces no clinical symptoms, or the symptoms are at most slight."

Ewing[11] records two cases of pernicious anaemia in which postmortem there was very tight stenosis of the pylorus which admitted a pencil with difficulty. The mucosa showed the changes of well marked chronic gastritis but the constriction was the result of chronic inflamatory change - not of cancer. I have myself seen only one case which during life seemed to be a typical pernicious anaemia and which postmortem showed a small carcinoma of the pylorus. This case would seem to agree with Ehrlich's description, for here the carcinoma produced no symptoms, and from its appearance postmortem, it evidently was not the cause of death. On the other hand I have repeatedly examined the blood of patients known to be suffering from carcinoma of the stomach, and have always found it to differ very materially from the blood of pernicious anaemia. Banti, Jurgens, and others have suggested "neurotic atrophy" of the intestinal mucosa as an important factor in the causation of pernicious anaemia and they support this view by the finding of degenerative changes in the ganglion cells of Meissner's and Auerbach's plexuses, but it has since been proved that such changes in the plexuses occur in numerous other diseases. Perhaps the most important investigations regarding the gastrointestinal tract as the origin of the disease are those of Hunter. He re-

gards the disease as being due to an infection with streptococci which gain an entrance by means of decayed teeth, chronic glossitis, or gastroenteritis. In case 9 where the gangrene set in on the gums and cheek, the process apparently started around the root of a decayed tooth, while in case 10 the very definite ulcers or abrasions on the tongue and tonsils may have served for the entrance of the organisms, if this theory of Hunter's be correct. Hunter's claim, however, has not been generally accepted, and the observations of McCrae in America who found oral sepsis rarer in some forty cases of pernicious anaemia which he examined, than in the average hospital patient, do not coincide with this theory.

Myelogenous Origin.-

Several cases of sarcoma affecting the bone marrow have been reported by Grawitz[12] and others, in which the blood changes closely resembled those of pernicious anaemia but the general idea at present is that the change of fatty marrow into red marrow which so constantly occurs in this disease has nothing to do with the aetiology of the disease and this view is strengthened by the few rare cases, of which case 9 is an example, in which there was almost complete atrophy of the marrow.

Nervous System.-

The implication of the nervous system in so many cases of pernicious anaemia has led some observers to look to the nervous system for the primary cause of the disease, but so far no characteristic changes have been found, and the result of the investigations has been to show that the changes in the central nervous system can all be explained as the result of the anaemia. Psychic influences even, have been mentioned as a probable cause, and it has been stated that in some cases patients can trace the origin of their symptoms to some intense emotion, but I have never found anything in any of the histories to corroborate this view. Curtin[13] reports two cases in females where the origin was attributed to severe mental shock, but at the most, such a factor can be regarded only as a predisposing agent, since we know of no definite action of psychic influences on the blood.

Organismal.-

Several years ago investigators have sought to trace the origin of pernicious anaemia to some organism, and so to add it to the list of infectious diseases. In 1883 Frankenhauser and Petrone[14] reported finding a form of leptothrix in several cases while in 1892 Klebs described the presence of flagellate

bodies in the fresh blood of advanced cases. Others claim to have isolated a bacillus from the blood but these observations have not been confirmed by more recent writers.

These, so far, have been the lines along which most of the investigations have been carried out regarding the aetiology of pernicious anaemia, but a study of the history of the cases makes it very evident that no one of these assumed causes will apply to all, and in the great majority of the cases both the history and the actual condition of the patient as revealed by examination give no clue whatever as to the origin of the disease.

Before considering the disease further it may now be well to record the following cases. I intend to deal with these cases more from the clinical than the pathological standpoint, and those few which present rather unusual symptoms I propose to go into more fully, while only the important points of the others will be dealt with.

Case. 1.

R. S. aet 42. male, commercial traveller; was first seen by Dr. Gulland in early spring of 1905. He was then very anaemic. Haemoglobin registered 48%. On iron and arsenic he improved in two months

and when next seen the Hb had risen to 105%. Three months later it had fallen to 50% and on iron alone it rose again to 80%. He was not seen again for several months and he then complained that for some weeks back he had been getting blind. His eyes were examined by Dr. Sinclair who reported a paracentral scotoma of both eyes; he had now also some difficulty in walking - his knee jerks were exaggerated - plantar reflex caused flexion - there was slight Rombergism; eyes reacted normally to light and to accommodation. There were no sensory changes, but there was tenderness over the calves; and muscles of thighs and legs were soft and flabby. He could not read, and he saw persons blurred. There were no fundal changes.

Blood film showed many megaloblasts and megalocytes: marked granular degeneration of reds, and polychromasia.

R.B.C. 2,780,000
Hb.....80%
C.I. ...1.4
W.B.C. ..3,900.

About a month later he was admitted to Chalmers Hospital suffering from acute pneumonia to which he succumbed after two days illness. No postmortem was allowed.

Case. 2.

Mrs. G. aet 56. was admitted to Chalmers Hospital on 13th January 1906, complaining of shortness of breath and palpitation. About six years ago she was "run down" and she suffered greatly from her stomach. She was treated for 14 days with rest in bed and kept on Benger's food and she improved sufficiently to be able to go about, although she did not feel strong. Ever since then she has had relapses at frequent intervals but has always picked up again with rest and dietary treatment. With each relapse she has complained of indigestion, weakness, and shortness of breath, palpitation and pain over the heart. She has been under medical observation during most of the six years but her blood had never been examined and evidently the real nature of her disease had not been suspected.

Previously she had not been very robust but she had never had any serious illness. Nothing of importance in the family history. She had one child twenty years ago and had an easy uncomplicated labour.

On admission, patient was very feeble - she had an anaemic appearance - complained of slight dyspnoea and there was slight oedema of the feet.

She remained five weeks in hospital and below are tabulated the blood counts and the weight taken

weekly. During her stay in hospital the temperature curve showed slight irregular pyrexia at night without any apparent cause and with no definite relation to the general symptoms or to the condition of the blood. The heart was not dilated but there were systolic murmurs at both mitral and pulmonary areas. Pulse was quite regular and average rate about 90. She had no sickness or dirrhoea. Liver was slightly enlarged. Spleen not enlarged. Stomach was not dilated. No nervous symptoms. Urine gave a well marked indican reaction but showed no abnormal constituents. She was put on the routine treatment which all cases received in hospital - namely, rectal irrigation with saline every morning - farinaceous diet - rest in bed - and arsenic.

She had at first 3 m of Liq. arsenicalis 4 times daily after food and this was gradually increased to 7m but at that stage she began to have gastric symptoms and the drug was consequently not pushed further.

Date.	R. B. C.	W. B. C.	Hb	Colour Index
13/1/06	1,700,000	5,800	45%	1.3
22/1/06	1,600,000	6,000	45%	1.4
30/1/06	2,160,000	5,800	50%	1.1
9/2/06	2,900,000	6,600	55%	.9
18/2/06	3,470,000	5,200	65%	.9

Films showed several megaloblasts; numerous megalocytes, polychromasia and a few reds showing granular degeneration.

Weight:-

13/1/06	6st.	12½ lbs.
20/1/06	6st.	10½ lbs.
27/1/06	6st.	11 lbs.
3/2/06	6st.	9 lbs.
10/2/06	6st.	6 lbs.
17/2/06	6st.	6 lbs.

Patient left hospital feeling much better. She has returned several times to report herself and her only complaint has been that on exertion she is still occasionally troubled with dyspnoea. Four months after leaving hospital her blood was examined and the following was the count:-

R.B.C.	3,800,000
W.B.C.	5,400
Hb.	70%
C.I.	.9

She did not continue the arsenic after leaving hospital, nor did she have the rectal irrigation but she still continued to live on farinaceous and light diet.

Case. 3.

J.A., minister, aet 50: was admitted to Chalmers Hospital on January 20th 1906, in a comatose condition. He remained comatose for several hours and on regaining consciousness he could not articulate properly for about an hour, and then his speech gradually became quite clear. There was no paralysis of the limbs. Before admission he was seen first by Dr.

Gulland in July 1905 when he was suffering from weakness and shortness of breath. Examination of the blood at that time revealed:

R.B.C. 3,500,000

W.B.C. 5,000 { Polymorphs 76% / Lymphocytes 22% / Eosinophiles 2%

Hb. 80%
Colour Index 1.01

Film showed no megaloblasts, several megalocytes and no granular degeneration. On July 27th 1905 R.B.C. were 3,228,000; Hb. 22%; W.B.C.6,000; CI 1.2. He was not again seen till he was admitted to hospital as mentioned above. He recovered completely from the comatose condition. There was no abnormal constituents in the urine. Fundus showed no changes. There was no subjective symptoms referable to the alimentary system. No cardiac murmurs could be heard. Knee jerks were sluggish - there was no plantar response at first and later it caused flexion.

On admission R.B.C. 2,670,000
W.B.C. 7,200
Hb. 66%
C.I. 1.2

Patient was then put on light diet and given 3m of arsenic 4 times daily after food. One week later blood was

R.B.C. 2,900,000
W.B.C. 7,200
Hb. 70%
C.I. 1.2

At the end of the second week patient felt very much better and was able to leave hospital.

His	R.B.C.	were then	3,140,000
	W.B.C.	" "	7,000
	Hb.	was "	70%
	C.I.	" "	1.1

He was again seen on 8th February 1906 when the blood count was:-

R.B.C.	2,480,000
W.B.C.	7,600
Hb.	58%
C.I.	1.2

He was not seen again nor his blood examined after that date but I believe that he has since died from apoplexy with aphasia.

Case 4.

The following is an interesting case because of the marked predominence of symptoms pointing to involvement of the nervous system. The nervous symptoms were so marked as almost to mask the real nature of the disease. Mrs. E. aet 35 - married - nullipara was admitted to hospital complaining of general weakness with loss of power in the arms and legs. She stated that six months ago while in South Africa she noticed that she was losing power in the arms and legs and she was unable to handle, or pick up things with her fingers. Frequently she had sensations of pins and needles in her fingers when she touched anything

cold. Later on, she lost sensation in her legs both to touch and to cold. This continued for about a month during which time she was not confined to bed. At the end of that time she felt so exhausted that she had to lie up and she became very ill and was delirious for ten days. On regaining consciousness she could not articulate properly and she was unable to move her legs or arms. The speech slowly recovered and a month later she started for this country. She did not improve on the voyage and on arrival she still complained of weakness and curious sensations in the soles of the feet. She had also a foul vaginal discharge and was curetted before being admitted to Chalmers Hospital.

She had previously suffered from rheumatism and pleurisy but was otherwise healthy.

On admission patient was very weak and had an apathetic appearance. Countenance was pale yellowish and muscularity was fair.

Nervous System:-

P. was very intelligent; memory unimpaired; very emotional; Speech rather slow but quite articulate.

Motor:-

She can walk with help. Legs drag slightly. She can move the legs in bed against considerable

resistance but there was some stiffness at the knees and ankles. She cannot raise the arms above the head, but she can flex and extend the wrists and elbows slightly and also the fingers. She has double drop wrist. She can abduct and adduct the fingers. There is some wasting of the thenar and hypothenar eminences and there is slight drop foot.

Sensory:-

Hyperaesthesia all over the body.

Pain on pressure over the calves.

Sensation to heat and cold unimpaired.

Reflexes:-

Knee jerks absent.

No ankle clonus.

Plantar reflex causes flexion.

The pupils reach slightly both to light and to accomodation.

Circulatory:-

Patient is breathless and suffers from palpitation.

Pulse 100, regular, and of rather low tension.

Heart sounds closed. Second sound accentuated in mitral and pulmonary areas.

Alimentary:-

No subjective symptoms. Tongue clean. Teeth good. Very constipated. Poor appetite.

Stomach not dilated. Liver and Spleen not enlarged.

Urine:-

Acid 1020. No abnormal constituents.

Indican reaction well marked.

Blood:-

Film showed numerous megaloblasts and megalocytes: well marked poikilocytosis and a few corpuscles showing granular degeneration.

Treatment:-. Patient was kept absolutely at rest in bed for a few days and then massage and electricity were applied to the legs and arms. She began to improve under this treatment and then she had 6 minims of Tinct. Nucis Vomicae thrice daily. She never had any arsenic during her stay in hospital. She was kept at first on farinaceous diet and later on light diet. She had also rectal irrigation with saline every morning. She was much troubled with sleeplessness and occasionally required veronal.

The following table shows improvement which took place in the blood.

24/1/06	R.B.C.	2,100,000
	W.B.C.	7,000
	Hb.	49%
	C.I.	1.1+
1/2/06	R.B.C.	2,070,000
	W.B.C.	6,400
	Hb.	46%
	C.I.	1.15

10/2/06	R.B.C.	2,510,000
	W.B.C.	7,900
	Hb.	55%
	C.I.	1.1
19/2/06	R.B.C.	2,680,000
	W.B.C.	5,800
	Hb.	60%
	C.I.	1.1
1/3/06	R.B.C.	3,210,000
	W.B.C.	6,200
	Hb.	65%
	C.I.	1

Film then showed a few megaloblasts and some granular degeneration of the reds.

The temperature was practically normal throughout with only an occasional evening rise without any evident cause.

About a month after leaving hospital patient was again seen when her nervous symptoms had again got much worse and her blood count showed:-

R.B.C.	1,856,000
W.B.C.	4,800
Hb.	50%
C.I.	1.4

She did not then wish to be readmitted to hospital and I have not been able to trace her further history.

Case 5.

W.W., Male, aet 53. Shepherd. Was admitted to hospital on April 16th 1906 complaining of general weakness and shortness of breath. Twelve months prev-

iously he began to feel weak and easily tired out. He was also very short of breath on the least exertion, and sufferred greatly from pain over the heart. He consulted his doctor who gave him some medicine. He improved in ~~in~~ general health for some time and was able to go about his usual work, although feeling rather feeble. ~~Before~~ two months before admission he became very weak and he again consulted his doctor who examined his blood and diagnosed pernicious anaemia and advised his removal to hospital.

Patient had always previously been healthy and there was nothing of note in the family history. He was a well developed fairly muscular man. There was a lemon yellow tint of the skin and the mucus membranes were very anaemic.

Circulatory:-

He was breathless on the least exertion: often felt faint and was troubled with palpitation. There was slight oedema of feet.

Pulse 90. regular - low tension - no arterial thickening. Systolic bruits were heard at all cardiac areas. Heart was not dilated.

Alimentary:-

Appetite fair; teeth good; tongue clean; gums fauces and pharynx anaemic. Bowels constipated. Liver enlarged and extends about an inch below

the Costal margin. Spleen is not enlarged.

Patient had a test breakfast given repeatedly and in every instance the amount of free hydrochloric acid was found to be diminished; the average amount present being .1 H.Cl. It was never however on any occasion entirely absent.

Nervous System:-

No subjective symptoms. Reflexes normal. Pupils react to light and to accommodation.

Treatment.- He was kept on light diet during his stay in hospital and had rectal irrigation each morning.

He was also put on arsenic: the dose being increased from 3 to 9 minims 4 times a day but at that stage he began to show gastric symptoms and the arsenic was not pushed further. It was given in combination with sodium bicarbonate latterly but even then he could not tolerate the larger doses.

The following tables show the condition of the blood and also the body weight during the time he was under treatment:-

18/4/06	R.B.C.	1,370,000		
	W.B.C.	7,400	Lymphocytes	39%
			Polymorphs	59%
			Eosinophils	1%
			Basophils	1%
	Hb.	45%		
	C.I.	1.4		
24/4/06	R.B.C.	2,210,000		
	W.B.C.	7,600	Lymphocytes	42%
			Polymorphs	57%
			Basophils	1%
	Hb.	55%		
	C.I.	1.2		
1/5/06	R.B.C.	2,580,000		
	W.B.C.	6,200	Lymphocytes	44%
			Polymorphs	56%
	Hb.	65%		
	C.I.	1.25		
8/5/06	R.B.C.	2,800,000		
	W.B.C.	6,000	Lymphocytes	48%
			Polymorphs	51%
			Basophils	.5%
			Eosinophils	.5%
	Hb.	65%		
	C.I.	1.15		
15/5/06	R.B.C.	2,300,000		
	W.B.C.	6,000	Lymphocytes	42%
			Polymorphs	48%
	Hb.	50%		
	C.I.	1.08		
21/5/06	R.B.C.	3,760,000		
	W.B.C.	6,500		
	Hb.	60%		
	C.I.	.8		
30/5/06	R.B.C.	3,840,000		
	W.B.C.	4,400	Lymphocytes	45%
			Polymorphs	55%
	Hb.	65%		
	C.I.	.8		

Weight.

16/4/06.	11st 12 lbs	14/5/06	11 st 6½ lbs.
23/4/06.	11st 12 lbs.	21/5/06.	11 st 4 lbs.
30/4/06.	11st 7 lbs.	28/5/06.	11 st 3 lbs.
7/5/06.	11st 7 lbs.	4/6/06.	10 st 12 lbs.

Patient was allowed up about a week before leaving hospital and was able to move about freely but still felt rather easily tired.

He returned to his home in the country and when last heard of he had remained well. He was instructed on leaving, to keep to light diet and if ever he began to feel the symptoms return he was advised to begin the arsenic under his doctor's directions but otherwise he was not to continue taking the arsenic.

Case 6.

T.C., male, aet 37 was admitted on 26th March complaining of general weakness and pains in the stomach. For some months back he had felt himself getting weaker. Four months ago he first complained of pain in the stomach. He vomited after almost every meal and he had a good deal of abdominal pain and discomfort for some time after taking food. He was under treatment for stomach trouble but he did not improve and he became gradually weaker and later began to complain of shortness of breath after the least exertion.

Apart from having scarlet fever in childhood he had always been healthy. His father died of septicaemia. On admission patient had a listless expression and a yellowish countenance. His temperature ranged from 99° to 100° F. for several days but eventually settled down to about normal with only occasional evening rises.

Alimentary:-

Subjective symptoms as in history.

The stomach was not dilated. Liver was slightly enlarged and lower border could be felt as a firm edge just below the costal margin. Spleen was not enlarged. Bowels had been very costive before admission. A test breakfast was given on several different occasions and the amount of free hydrochloric acid was always diminished but never entirely absent. The average amount present was .12 H.Cl.

Circulatory:-

He complained of slight dyspnoca on exertion. There was slight oedema of the ankles. Systolic murmurs were heard at all the cardiac areas. Heart was not dilated. Pulse rate averaged about 100 and was regular but of rather low tension.

Nervous System:-

No subjective symptoms. Reflexes normal.

Urinary:-

Urine showed nothing abnormal except that the indican reaction was invariably well marked during his whole stay in hospital. There was never any albumen present.

Blood:-

Film showed a few megaloblasts, megalocytes and granular degeneration of reds.

28/3/06	R.B.C	2,330,000		
	W.B.C.	7,200	Polymorphs	55%
			Lymphocytes	44%
			Basophils	1%
	Hb.	45%		
	C.I.	.9+		
8/4/06	R.B.C.	2,100,000		
	W.B.C.	9,200	Polymorphs	50%
			Lymphocytes	48%
			Eosinophils	1%
			Basophils	1%
	Hb.	40%		
	C.I.	.9+		
18/4/06	R.B.C.	2,900,000		
	W.B.C.	13,200	Polymorphs	60%
			Lymphocytes	38%
			Basophils	2%
	Hb.	55%		
	C.I.	.9		

About this time patient was suffering from what was evidently an attack of influenza. His temperature remained about 101° - 102° for some days and the leucocytes were increased and it is interesting to note the increase in the proportion of the polymorphs.

28/4/06	R.B.C.	3,630,000	
	W.B.C.	12,800	P. 55% L. 44% B. 5% E. 5%
	Hb.	70%	
	C.I.	.9+	
3/5/06	R.B.C.	3,400,000	
	W.B.C.	12,000	P. 45% L. 55%
	Hb.	70%	
	C.I.	1.02	
10/5/06	R.B.C.	4,000,000	
	W.B.C.	6,500	P. 43% L. 56% B. 1%
	Hb.	85%	
	C.I.	.1+	

Weight:-

28/3/06	9 st. 10 lbs.
4/4/06	9 st. 6lbs .
11/4/06	9 st. 3 lbs.
18/4/06	9 st. 3 lbs.
25/4/06	9 st. 3½ lbs.
3/5/ 06	9 st. 4 lbs.
10/5/06	9 st. 4 lbs.

Treatment:-

Patient was kept in bed and had at first farinaceous and later light diet. He had also rectal irrigation with saline each morning. After the first week he had liquor arsenicalis four times daily after meals in doses increasing gradually from 2 to 9 minims.

At that stage he began to complain of slight neuritis in the legs and the arsenic had to be stopped for a few days and then begun again, but

it was found impossible to push the dose further.

He had practically no stomach symptoms while in hospital and his only complaint was general weakness. On leaving hospital he went to the country for a month and at the end of that time he reported himself at hospital when his blood count showed:-

R.B.C.	4,200,000
W.B.C.	5,000
Hb.	80%
C.I.	.9+

Film showed no megaloblasts, several megalocytes and a few cells showing granular degeneration of the reds. While in the country he had had plenty of milk and eggs but no meat and he gained about half a stone after leaving hospital.

Case 7.

W.P., aet 50, miner, was admitted first to hospital on 21st November 1905 complaining of general weakness. Six months previously he had to give up work because he felt too weak. He had always been able to go about till admission to hospital, but he became very breathless after the least exertion. One day he would feel fairly fit while the next day he might be perfectly exhausted. He was treated by his doctor for general debility and although he had various tonics he did not improve.

He had scarlet fever in childhood and had been a fairly heavy drinker for years. He had not had syphilis. His father died of epistaxis aged 62: his mother of diarrhoea aet 68. One child died from phthisis aged 19.

On admission patient was a poorly developed man. There was marked pallor of skin and mucous membranes. Gums were soft and bled easily. There was very slight oedema of the ankles.

Circulatory:-

Patient was very breathless on exertion and suffered from palpitation and dizziness.

Pulse was 96 per minute, regular, and of moderate tension. There was no thickening of the arteries. Systolic murmurs were heard all over the heart.

Alimentary:-

Patient suffered occasionally from sickness and vomiting and had also frequent attacks of diarrhoea. Liver was slightly enlarged. Test breakfast frequently repeated showed on each occasion an entire absence of free hydrochloric acid. There were no organic acids present.

Nervous:-

He complained of shooting pains in the legs. His walking was slightly ataxic and he had

difficulty in turning.

Romberism was well marked.

Knee jerks were absent on both sides. Right pupil was slightly larger than the left, and both reacted to light and to accommodation.

Urine:-

Showed no albumen. Indican reaction marked.

Blood:-

Film showed megalocytes and microcytes with polychromasia and poikilocytosis. No megaloblasts or normablasts were seen.

28/1105	R.B.C.	1,700,000	
	W.B.C.	4,800	P. 40% L. 59% B. 1%
	Hb.	35%	
	C.I.	1.03	
8/12/05	R.B.C.	1,620,000	
	W.B.C.	4,200	P.42% L.58%
	Hb.	35%	
	C.I.	1.02	
13/12/05	R.B.C.	1,570,000	
	W.B.C.	4,400	P. 48% L. 51% B. 1%
	Hb.	34%	
	C.I.	1.03	
20/12/05	R.B.C.	1,600,000	
	W.B.C.	4,300	P. 50% L. 50%
	Hb.	32%	
	C.I.	1.	

28/12/05.	R.B.C.	1,150,000	
	W.B.C.	4,000	P. 45% L. 54% E. 1%
	Hb.	30%	
	C.I.	1.3	
3/1/06	R.B.C.	1,490,000	
	W.B.C.	4,600	P. 42% L. 58%
	Hb.	35%	
	C.I.	1.25	
11/1/06	R.B.C.	2,490,000	
	W.B.C.	5,000	P. 50% L. 49% B. 1%
	Hb.	35%	
	C.I.	.9	
19/1/06	R.B.C.	2,930,000	
	W.B.C.	4,900	P. 43% L. 56% E. 5% B. 5%
	Hb.	50%	
	C.I.	.9	
29/1/06	R.B.C.	3,000,000	
	W.B.C.	4,600	P. 48% L. 52%
	Hb.	50%	
	C.I.	.89	
10/2/06	R.B.C.	3,400,000	
	W.B.C.	4,600	P. 48% L. 52%
	Hb.	55%	
	C.I.	.8	

Progress and Treatment:-

Patient was at first treated with bone marrow but this seemed to cause sickness and diarrhoea and had eventually to be stopped. Arsenic was then begun and he was able to get up to 10 minims 4 times

daily. he was restricted to farinacious diet and had rectal irrigation each morning. During his stay in hospital he had three very severe attacks of epistaxis and on one occasion the posterior nares had to be plugged. These attacks seemed to come on without any warning and without any evident cause. He had no haemorrhages into the skin nor did he have any haemorrhages from the bowels. The nervous symptoms did not improve appreciably although he had strychnine hypodermically and electricity applied to the legs.

The following table shows his weekly weight:-

21/11/05	9 st.	8 lbs.
29/11/05	9 st.	3 lbs.
6/12/05	9 st.	4 lbs.
13/12/05	9 st.	7 lbs.
20/12/05	9 st.	5 lbs.
27/12/05	9 st.	5 lbs.
2/1/ 06	9 st.	7½ lbs.
9/1/ 06	9 st.	7 lbs.
16/1/ 06	9 st.	7 lbs.
23/1/ 06	9 st.	9 lbs.
30/1/ 06	9 st.	11½ lbs.

Patient returned to report himself three months later. He had had several attacks of epistaxis since leaving hospital. He did well for two months after his discharge and then weighed 10 st. 10 lbs., but during the last month he had fallen back and at date of reporting himself he weighed 9 st 9 lbs. He had also greater difficulty in walking and he very easily became exhausted.

Blood film showed one megaloblast, megalocytes, poikilocytosis and granular degeneration of reds.

R.B.C. were 2,740,000
W.B.C. " 5,000
Hb. " 60%
C.I. " 1.05

He was advised to return to hospital but was unable for domestic reasons to do so.

Case 8.

J.D., male, aet 23, Bookseller, was admitted on 11th April 1906 complaining of general weakness. He had been feeling weak and easily tired for months previously, but before admission he felt so exhausted one morning that he could not rise out of bed. He consulted his doctor who said he was run down and gave him a tonic. He tried to do his usual work on the following day but became so faint and tired that he had to go home to bed. He remained in bed for a week during which time he had slight diarrhoea. He again tried to start work but was so weak that he had to give in and he was then advised to come to hospital. He had never had any haemorrhages.

He had scarlet fever when he was 9 years old and after that his hair turned white and has remained so. He was operated on for inguinal hernia nine years ago.

His father died of pernicious anaemia aet 50, and

his mother of enlarged liver aet 38. A brother and a sister died of scarlet fever.

On admission patient was extremely pale and had an anxious expression. He had a good head of hair which was almost white. The mucus membranes were very pale: the skin showed no evidences of haemorrhages.

Circulatory:-

Complained of shortness of breath, faintness and palpitation. Pulse rate averaged 80 to 90- regular and of low tension.

There was well marked venous pulsation in the neck. Systolic bruits heard all over the cardiac areas. There was slight dilatation of the right heart. There was no varicose veins and no dropsy.

Alimentary:-

Had occasional diarrhoea. Tongue slightly furred. Artificial teeth. Gums, fauces and pharynx very anaemic. Stomach was not dilated. Liver could just be felt below the costal margin. Spleen was not enlarged. A test breakfast was given frequently and on each occasion there was found to be no free hydrochloric acid.

Urinary:-

Indican reaction well marked. No abnormal constituents.

Nervous System:-

No subjective symptoms. Knee jerks diminished. Pupils react normally to light and to accomodation.

Blood:-

Film showed megaloblasts, megalocytes, poikilocytes, polychromasia and granular degeneration of the reds. A megaloblast with dividing nucleus was seen in the film.

Progress and Treatment:-

For the first fortnight there were irregular rises of temperature up to 99° or 100° F. but afterwards the temperature settled down and showed no marked rise. He was kept at rest in bed and had rectal irrigation daily. He had Fowler's solution at first in two minim doses 4 times daily and this was gradually increased to 7 minims. He was kept on farinaceous diet. He made fair progress till about the middle of May when he began to be very sick and complained of great pain across the stomach and bowels. He had also occasional diarrhoea. The arsenic was then stopped for a time and he was put on hydrochloric acid 20 m. after food repeated every ten minutes for three doses. He had also gastric lavage every night and this gave him great

relief. After about a week he was put on the acid solution of arsenic after meals and this seemed to agree better than Fowler's solution. He began to put on weight and in every way he improved and by the beginning of June he was able to leave hospital feeling very much better. The following table shows the variations in the blood count in the different weeks and these variations were found to coincide closely with the general condition of the patient although the cause was not always apparent.

14/4/06	R.B.C.	2,670,000	
	W.B.C.	4,600	P. 40% E. 1% L. 54%
	Hb.	65%	
	C. I.	1.2	
20/4/06	R.B.C.	2,890,000	
	W.B.C.	4,100	P. 45% M. 1% L. 54%
	Hb.	1.1+	
28/4/06	R.B.C.	3,180,000	
	W.B.C.	5,000	P. 42% E. 1% B. 1% L. 56%
	Hb.	65%	
	C.I.	1.03	
4/5/06	R.B.C.	3,480,000	
	W.B.C.	5,000	P. 40% M. 1% L. 55%
	Hb.	60%	
	C.I.	1.2	

11/5/06	R.B.C.	2,960,000	
	W.B.C.	4,000	P. 38% E. 1% L. 61%
	Hb.	60%	
	C.I.	1.01	
18/5/06	R.B.C.	2,600,000	
	W.B.C.	4,000	P. 39% L. 61%
	Hb.	55%	
	C.I.	1.04	
26/5/06	R.B.C.	3,020,000	
	W.B.C.	5,000	P. 42% E. 1% M. 1% L. 56%
	Hb.	60%	
	C.I.	1.	
2/6/06	R.B.C.	3,440,000	
	W.B.C.	4,000	P. 49% L. 51%
	Hb.	65%	
	C.I.	.9+	
8/6/06	R.B.C.	3,700,000	
	W.H.B.	4,500	P. 52% E. 1% L. 47%
	Hb.	70%	
	C.I.	.9	

Films always showed much the same characteristics, and even just before leaving hospital a megaloblast could always be got in each film. A few eosinophile myelocytes were also seen.

Weight.

11/4/06	8 st.	5½ lbs.
18/4/06	7 st.	13½ lbs.
25/4/06	8 st.	3½ lbs.
2/5/06	8 st.	8½ lbs.
9/5/06	8 st.	5½ lbs.
16/5/06	8 st.	Sickness and diarrhoea. Stomach washed out.
23/5/05	8 st.	

30/5/06	8 st.	6½ lbs.
7/6/06	8 st.	8 lbs.
14/6/06	8 st.	7 lbs.

On leaving hospital patient went to the country for a month. While there he took plenty of fresh eggs and milk, but no meat, and he lived in the open air as much as possible. He reported himself at the end of the month. He then weighed 9 st. 3 lbs. His blood count showed:-

R.B.C	3,800,000
W.B.C.	5,000
Hb.	75%
C.I.	.9+

Films showed numerous megalocytes and one megaloblast. He remained at work for about two months, during which time he felt fairly well but on October 1st 1906 he was readmitted to hospital after having been in bed for a week with diarrhoea. On admission he looked very ill but complained of no pain. Diarrhoea had by this time stopped. He was put on farinaceous diet, saline irrigation and 3 minims of Fowler's solution four times daily. He again had several test breakfasts and on each occasion there was an entire absence of free hydrochloric acid. Therewas no oedema of feet or lungs. His temperature varied from 99 to 101° and was never normal. He remained in much the same condition for a week during which time he had only one attack of diarrhoea which was checked by large doses of Bismuth. He gradually

became weaker but complained of nothing but the weakness. Temperature now remained constantly between 100° and 101° F. On 18th October the arsenic was stopped and he was given Liquor. Hydrarg. perchlor. m 60 t.i.d. as an antiseptic but this seemed to cause sickness and was stopped next day. He was then put on Bismuth salicylate and Salol āā gr. X but the sickness still continued. Gastric lavage did not as formerly give much relief. He looked very much exhausted and his blood as will be seen from the following table continued to deteriorate till he ultimately died. The temperature remained about 101° F. On the day of his death he was twice transfused, on each occasion two pints of saline being given intravenously and the pulse seemed to improve temporarily after the transfusion. He complained just before death of tightness in the chest and difficulty of breathing but no definite complications could be made out, except considerable oedema at both bases.

Blood Table:-

5/10/06	R.B.C.	1,600,000	
	W.B.C.	3,200	P. 40% L. 58% E. 1% M. 1%
	Hb..	35%	
	C.I.	1.01	
8/10/06	R.B.C.	1,400,000	
	W.B.C.	3,000	P. 38% M. 2% L. 60%
	C.I.	1.07	

17/10/06	R.B.C.	1,100,000	
	W.B.C.	4,000	P. 38% M. 1% E. 1% L. 63%
	Hb.	25%	
	C.I.	1.1	
21/10/06	R.B.C.	700,000	
	W.B.C.	5,000	P. 45% M. 1% L. 54%
	Hb.	20%	
	C.I.	1.4	

Immediately after death two large syringefuls of 10% formalin were injected into the abdomen after the manner recommended by Faber and Bloch[15] who found in three cases in which that was done that there was no atrophy of the intestinal mucous membrane.

A postmertem examination was made about 12 hours after death and the following are the chief points of the examination.-

> Left pleural cavity dry - fibrous adhesions at apex posteriorly and at lower lobe of left lung. Lower lobe of left lung congested and oedematous but crepitant throughout.
> Emphysema at apex and anterior margin of upper lobe.
> Right pleural cavity contained small quantity of fluid. No adhesions. Glands at root of right lung not enlarged. Viscid mucus in larger bronchi. Small pigmented glands at root. Emphysema at apex and anterior margin. Congestion and oedema at base but no pneumonia.

Pericardium:-

Contains excess of clear fluid. Blood is extremely thin and watery. Heart shows excess of fat on surface. No haemorrhages. Right auricle is slightly dilated and empty. Right ventricle is empty. Pulmonary valves competent. Tricuspid and pulmonary cusps nothing abnormal. Left auricle slightly dilated and empty. Mitral orifice distinctly dilated. Aortic valve competant. Mitral and aortic cusps show nothing abnormal. Left ventricle is distinctly dilated. Heart walls show well marked fatty degeneration.

Spleen:-

Is enlarged and firm. On section it shows a dark red colour. There is apparent increase of stroma and thickening of vessels. Malphigian bodies are not distinct.

Liver:-

Is slightly enlarged, yellowish brown on surface, and shows well marked fatty degeneration and chronic venous congestion. When treated with Potass, ferrocyanide and hydrochloric acid it gives a very marked iron reaction. This was also present to less extent in the spleen. Stained sections of liver under the microscope also show the presence of iron in large excess.

Gallbladder:-

Is small and contains small quantity of viscid bile.

Stomach:-

Is not dilated. Stomach contains small blood clots. No evidence of ulcer. Mucous membrane both naked eye and microscopically shows no atr atrophy.

Small Intestine:-

Small petechial spots are present in lower part of small intestine. Pieces were removed from different parts of the intestine and examined naked eye and microscopically. Only one portion from near the caecal end showed any atrophy of mucous membrane.

Large Intestine:j

Mucous membrane healthy.

Kidneys:-

Pale and firm. Base of pyramids congested. Well marked fatty change. No distinct thickening of vessels. Give iron reaction.

Haemolymph glands very numerous on posterior wall of abdomen. Pancreas appears normal. Suprarenals normal. Thyroid normal. Marrow of ribs and of femur shows well marked transformation into red marrow. Film of marrow shows numerous megaloblasts, leucocytes and several macrophages e.g. large mononuclear lymphocytes containing several red corpuscles within their cell body. Brain and spinal cord were not examined.

Case 9.

The following case belongs to that rare group of cases known as aplastic pernicious anaemia in which the chief characteristic found postmortem is complete atrophy of the bone marrow. I have been able to find reported in recent literature only a very few instances of such cases and because of their rarity I have made below a summary of the notes of some of these cases for comparison with the present case.

Pasteur[16] reports the case of a man aet 34 who complained of weakness and bleeding from the gums. There was no lemon tint of skin, no febrile exacerbations and no indicanuria. The disease ran a rapid course. The patient became progressively weaker and died in nine weeks.

> The Red Blood Corpuscles numbered 1,500,000
> " White " " " 5,400
> Lymphocytes 60%
> and the Hb. was 25% giving a colour index of .8
> No megaloblasts or normoblasts were seen in the films.

Postmortem:-

> Iron was found in liver in abundance. No iron found in spleen, kidneys or brain. There was no hypertrophy of the marrow; films showed no nucleated reds, a few granular myelocytes.

Muir[17] reports the following case of a boy aet 14 who was admitted to hospital complaining of epistaxis, haematemesis and purpura. He had been healthy till one month before admission. Four days before admission haemorrhagic spots were noticed over the body. Two days before admission he had epistaxis and haematemesis. Nothing of note in family history. On admission - there was marked anaemia; oozing of blood from gums and several petechial spots on the body. At first he improved slightly but about a month after admission he had severe haematemesis and passed into a condition which ultimately proved fatal.

On 15th January R.B.C. were 800,000
W.B.C. " 7,000
Hb. " 12%
C.I. .75

On 9th February R.B.C. were 640,000
They showed variation in size, slight poikilocytes, practically no megalocytes and no nucleated reds. Relative lymphocytosis of 70%.

Postmortem:-

Heart.- Extensive fatty degeneration. Few petechiae in endocardium.

Stomach.- Extensive patchy haemorrhages.

Small Intestine.- also showed haemorrhages. No haemorrhages in Large Intestine. No ulcerations or abrasions in any part of the alimentary tract.

Liver.- Normal size - firm - iron present in considerable quantities in outer half of lobules. central part of lobules shows fatty degeneration

Spleen.- Slightly enlarged - firm - nothing abnormal - no iron.

Kidneys:- Pale - large amount of iron present. Pancreas and suprarenals fatty. Marrow of femur and ribs almost exclusively fat.

Microscopically.- There was fatty degeneration of the heart, kidneys, and liver. Iron reaction was not so well marked in sections as to naked eye.

Films of Marrow.- showed fat. R.B.C. very deficient, one or two nucleated reds. No eosinophils.

Commenting on the case he stated that he believed the condition of the marrow to be primary and that it had kept up the anaemia, and that as a result of some intercurrent condition the haemorrhage and purpura had occurred . He said he was familiar with

cases of pernicious anaemia where there was only feeble transformation of marrow into red marrow, but he had not met with any case of pernicious anaemia in the adult where there was an excess of fat in the marrow of the ribs.

Ehrlich[18] reported a case of fatal acute anaemia in a patient who suffered chiefly from metrorrhagia. The red cells were reduced to 215,000. Films showed mostly microcytes and there were no nucleated reds while postmortem there was found to be no hypertrophy of the marrow.

Ewing[6] reports the following case where the symptoms would seem to point to a similar condition but unfortunately no postmortem was obtained. The patient was a boy of 18, who had always been pale and whose sister was extremely pale and moderately anaemic. He suffered from uncontrollable epistaxis and finally from intestinal haemorrhages for three weeks before death. During the last week the red cells numbered 456,000; leucocytes were reduced in number, there were no megaloblasts and no megalocytes, the majority of the reds being oval and undersized. Ewing expresses a doubt as to whether such cases ought to be classed as acute pernicious anaemia and regards it as premature to draw from such cases any

conclusions regarding the pathological anatomy and pathogenesis of true pernicious anaemia.

I propose to discuss these views later when dealing with the symptoms and morbid anatomy of the disease and will now proceed to detail the somewhat similar case which came under my own observation.

M.G., female, 68 unmarried, was admitted to hospital on 25th May 1906 complaining of swelling of the feet and general weakness. She states that until three weeks ago she was perfectly well and about that time she began to notice that her feet were swollen at nights. The swelling disappeared in the morning but during the day she felt very tired and she became breathless after the least exertion. She had an attack of sickness and vomiting about this time which lasted 24 hours. She felt so weak that she had to give up her situation as domestic servant and for the last fortnight she had been confined to bed at home. She noticed a slight petechial rash on both legs about a week before admission. She has had no epistaxis or haematemesis. She was seen by the doctor who thought it a case of pernicious anaemia and recommended her removal to hospital. Except for scarlet fever in childhood she had never had a day's illness. There was nothing of note in family history.

On admission patient had a dark yellowish complexion and an apathetic expression. The lips and conjunctivae were pale but there was no oedema of eyelids. There was slight oedema of ankles and a faint petechial rash over the front of both tibiae.

Alimentary:-

No subjective symptoms. Fairly good appetite. Tongue is clean and moist. There are several bad teeth. Stomach is not dilated. Liver and spleen are not enlarged.

Nervous:-

Sleeps a great deal during the last three weeks. No subjective symptoms. Knee jerks increased. No ankle clonus. Plantar reflex causes flexion. Pupils react slightly both to light and to accomodation.

Circulatory:-

No pain or palpitation while at rest. Shortness of breath only on exertion. Pulse 88. regular - very small expansion. No thickening of the arteries. Heart not dilated. Systolic bruit heard at mitral and pulmonary areas.

Urine:-

Pale clear coloured. Very often showed a deposit of uric acid crystals. Indican reaction well marked, no albumen, blood or sugar.

Blood:-

Film showed poikilocytosis, polychromasia one megaloblast, no megalocytes and relative lymphocytosis. Films taken at subsequent dates without exception showed neither megaloblasts nor megalocytes.

R.B.C. 1,200,000

W.B.C. 4000 { Polymorphs 48% / Lymphocytes 50% / Basophils 2% }

Hb. 30 %.

Progress and Treatment:-

Patient was at first put on the routine treat

ment - farinacious diet - rectal wash out; and arsenic - three minims of Fowler's solution four times daily after food. She lay quite listless in bed and spent the greater part of the day sleeping. She complained of nothing but weakness. Several test breakfasts were given and on each occasion there was a diminution of the amount of free hydrochloric acid, the average being .116 H.Cl. With the rest in bed the oedema of the feet diminished. After three days the arsenic was stopped and she was put on hydrochloric acid twenty minims after food.

On the 7th June she complained of a gumboil. The face was very much swollen. The left upper jaw contained a carious tooth and the swelling and ulceration had evidently started around the root of that tooth. The hydrochloric acid was now stopped and active treatment was applied to the ulceration in the mouth.

Two days later the face was much worse and on the inner side of the left cheek there was an extensive area of necrotic tissue. The sloughs were touched with pure carbolic and mouth swabbed out with Hydrogen Peroxide while patient washed the mouth frequently with boric lotion. The ulceration of the mouth caused practically no pain but only discomfort when swallowing. By the 14th June the mouth began to show signs of healing. The sloughs separated and the ulceration had ceased to spread. For a week her temperature had remained between 101° and 102° F. but now it came down to normal. The increase of polymorphs during this period as shown later in the table is interesting.

By the 19th June the mouth had practically healed and she was again started on arsenic three minims as before. She felt very feeble by this time but had no pain. She slept a great deal and often she had to be roused to take nourishment.

On 24th June both knee jerks were very much exaggerated and plantar reflex produced extension on both sides. There was no ankle clonus.

The pulse was then very feeble and she did not care to be roused for anything.

On the following day she was much feebler. Voice was feeble and tremulous. She could not move herself in bed. Double Babinski sign was still present.

Although sixty films were taken from the blood shortly before death no megaloblasts were found in any of these. She gradually became weaker and died about midnight.

Immediately after death the abdomen was injected with 10% Formalin.

A limited postmortem was allowed and the following are the chief points of the examination.

Lungs:-

Showed emphysema, congestion, and oedema. At base of right lung there were a few patches of commencing pneumonia. Glands at roots were pigmented but not caseous.

Pericardium:-

Contained no fluid.

Heart:-

Filled with antemortem pale clot. Right ventricle- walls thin and fatty. Papillary muscles show thrush-breast marking. Left ventricle - Thrush-breast marking extremely well seen.

Auricles.- Thin and dilated. There was slight thickening on the edges of the cusps of the auriclo-ventricular valves.

Pulmonary valves were normal. Aortic valves were slightly fatty.

Abdomen:-

Colon was V shaped extending down to three inches above the symphysis. Stomach was contracted. Mucous membrane appeared healthy and microscopically it showed no atrophy. Intestines were not distended except the colon which was ~~not~~ distended with gas. They contained a very small amount of faeces.

The bowel was only partially fixed with the formalin. Pieces were cut from the colon, the ileum, and from the jejunum. Microscopically

the mucus membrane from colon and ileum showed atrophy while that from the jejunum was healthy.

Spleen:

Was very small and showed increase of fibrous tissue. It did not give the iron reaction.

Liver:

Small and pale, adherent on right side to diaphragm. Gall-bladder distended with greenish black bile. No gall stones.

On section, liver was pale and fatty with slight increase of connective tissue. It gave well marked iron reaction.

Microscopically - sections showed large deposits of iron in the centre of the lobules.

Haemolymph Glands: small and not very numerous.

Mesenteric Glands: few and small.

Pancreas: rather small - appears to be normal.

Kidneys: adherent capsules.

Cortex: diminished irregularly - very pale.
Left suparental enlarged. Slight iron reaction
Very irregular distribution of pigment.
Right suparenal appears normal.

Thymus: Represented by large mass of fat.
No thymus tissue.

Thyroid: Rather small.
Cystic formation in apex of left lobe containing celloid material.

Marrow: of femur, ribs, and sternum was almost completely replaced by oedematous fat.

Films: Showed fat, leucocytes and no nucleated red blood corpuscles.

The following shows the condition of the blood during the few weeks patient was in hospital.

26/5/06	R.B.C.	1,200,000	
	W.B.C.	4,000	Polymorphs 48% Lymphocytes 50% Basophils. 2%
	Hb.	30%	
	CI.	1.25	
1/6/06	R.B.C.	1,300,000	
	W.B.C.	3,200	Polymorphs 36% Lymphocytes 62% Basophils 1%
	Hb.	30%	
	C.I.	1.15	
9/6/06	R.B.C.	1,500,000	Polymorphs 80%
	W.B.C.	10,000	Lymphocytes 18% Eosinophil 1% Myclocytes 1%
	Hb.	30%	
	C.I.	1	
15/6/06	R.B.C.	800,000	
	W.B.C	4,400	Polymorphs 49% Lymphocytes 51%
	Hb.	20%	
	C.I.	1.15	
24/6/06	R.B.C.	700,000	
	W.B.C.	8,000	Polymorphs 64% Lymphocytes 34% Eosinophil 1% Basophil 1%
	Hb.	18%	
	C.I.	1.4	

Case 10.

J.A., male, blacksmith, was admitted on 27th June 1906, complaining of general weakness.

About six months before admission patient had a severe haemorrhage from the rectum which his doctor said was due to bleeding piles. The bleeding lasted two days, and patient felt very weak for some time

after this but was able to continue at work till three months before admission when he caught a chill which laid him up with severe pains all over the body. From that time onward he has been very weak and unable to work. He has occasionally had pains across the stomach and bowels but has never had any vomiting or diarrhoea. About four days before admission he had a slight epistaxis without any apparent cause. During the last few weeks he has noticed his feet slightly swollen at nights, and he has been very short of breath on exertion. He had previously always been healthy and there was nothing of note in the family history.

On admission he had a very characteristic lemon yellow appearance and a dull expressionless countenance.

Alimentary:-

Subjective symptoms as in history.
Tongue was furred and showed several fissures in the transverse axis of the tongue. There were also several small superficial abrasions on the left tonsil and on the pillars of the left fauces. Stomach was not dilated.
Test meal showed deficiency but not entire absence of free hydrochloric acid. Average amount was .16 H.Cl.
Liver was slightly enlarged and lower border could be palpated just below the costal margin as a firm sharp edge. The spleen extended forward just to the anterior axilliary line.
There were several internal piles which were not inflamed.

Circulatory:-

Complained of dyspnoca and weakness on exertion. Had occasional palpitation. No cough or spit. Pulse was regular and of good tension. Rate averaged about 86. There was slight oedema of both ankles. Faint systolic murmurs could be heard at mitral and pulmonary areas. Heart was not dilated.

Urinary:-

Urine always gave well marked indican reaction. It contained no albumen, blood or sugar. Occasionally showed a deposit of uric acid crystals.

Nervous:-

No subjective symptoms. Knee jerks absent. No Argyll Robertson Phenomenon. No sensory changes. Gait unaffected.

Blood:-

Film showed megaloblasts, megalocytes, granular degeneration of the reds, Polychromasia and relative lymphocytosis. Several megaloblasts with mitotic nucleiwere from time to time seen.

Progress and Treatment:-

Patient was put on the routine treatment of farinaceaus diet, arsenic, rest in bed and rectal irrigation. In this case the acid solution of arsenic was used instead of Fowler's solution.

During the first month in hospital he made slow progress. About a month after admission he began to manifest cerebral symptoms especially at nights. He had the idea that everyone was taking about him and about his food. He on several occasions got up and dressed himself during the night intending to go home as he could not have everybody talking about him.

After considerable persuasion he could always be prevailed upon to return quietly to bed. He was much more sensible during the day although even at times he was quite irrational and often emotional. He had no fever during the manifestation of the cerebral symptoms. On August 23rd he had a rigor, T° reaching 101° F. and after it passed off he complained of nothing. A trace of albumen and some pus cou could now be detected in the urine. From then onwards till the day of his death he had several rigors, temperature on one occasion reaching 105° F. and in the intervals the temperature never came down to normal. As will be seen from the blood table he had no leucocytosis during this time but the proportion of polymorphs became increased. He complained latterly of pain over the heart and in the region of the left kidney. The pulse gradually became more rapid and feeble and patient was then kept on stimulants and heart tonics. There was evidence of pneumonia but about 8cc of clear fluid was aspirated from the left pleura shortly before death which took place on the 6th September 1906.

Blood Table:-

27/6/06	R.B.C.	1,150,000	
	W.B.C.	5,600	L. 58% P. 40% B. 1% E. 1%

27/6/06	Hb.	30%	
	C.I.	1.3	
5/7/06	R.B.C.	1,300,000	
	W.B.C.	4,000	L. 60% P. 39% B. 1%
	Hb.	35%	
	C.I.	1.3	
11/7/06	R.B.C.	1,800,000	
	W.B.C.	6,800	L. 55% P. 43% B. 1% E. 1%
	Hb.	40%	
	C.I.	1.1	
20/7/06	R.B.C.	2,200,000	
	W.B.C.	5,200	L. 58% P. 41% B. 5% E. 5%
	Hb.	45%	
	C.I.	1.001	
29/7/06	R.B.C.	2,800,000	
	W.B.C.	4,900	L. 53% P. 47%
	Hb.	55%	
	C.I.	.9	
7/8/06	R.B.C.	2,350,000	
	W.B.C.	5,200	L. 59% P. 40% E. 1%
	Hb.	50%	
	C.I.	1.01	
15/8/06	R.B.C.	2,760,000	
	W.B.C.	3,000	L. 58% P. 40% B. 1.5% E. .5%
	Hb.	50%	
	C.I.	.9	
22/8/06	R.B.C.	3,000,000	
	W.B.C.	3,000	L. 60% P. 39% E. 1%
	Hb.	55%	
	C.I.	.9	

29/8/06	R.B.C.	2,300,000	
	W.B.C.	2,800	L. 51% P. 49%
	Hb.	48%	
	C.I.	1.04	
4/9/06	R.B.C.	2,400,000	
	W.B.C	3,900	L. 42.3% P. 55.3% E. 1.2% B. 1.3%
	Hb.	50%	
	C.I.	1.04	
6/9/06	R.B.C.	2,000,000	
	W.B.C.	4,200	L. 43.1% P. 55.2% E. 1% B. .7%
	C.I.	1.1	

Weight per week:-

9 st. 2 lbs.
8 st. 13 lbs.
8 st. 11 lbs.
8 st. 11½lbs.
9 st. 1 lbs.
9 st. 5½lbs.
9 st 4 lbs.
9 st. 1lbs.
8 st. 11½ lbs.

No formaline was injected into the body, but the postmortem examination was made 6 hours after death and the following are the chief points in the examination:-

On surface of body were numerous petechiae mostly on trunk varying in size. On the left side just below the heart pus was found in the muscles, ~~but~~ which were not exceptionally pale. There was considerable ecchymosis round site of aspiration puncture.

Left pleural cavity contained some blood stained fluid.

There were some recent adhesions at the base.

Small abscess found just under the pleura

on lateral aspect of upper part of ~~of~~ lower lobe of left lung. Upper lobe very emphysematous.

Some recent pleurisy over lower lobe.

Right lung showed well marked emphysema and congestion. Deeply pigmented. Commencing bronchopneumonia in lower lobe.

Nothing special about bronchial glands on either side.

Pericardium contains some clear fluid.

Cardiac orifices and valves normal.

Wall shows thrush breast marking..

Small abscess in one of the papillary muscles of the left ventricle.

Liver:-

Normal in size, pale, slightly fatty - some chronic venous congestion and excess of fibrous tissue.

Iron reaction is present but not very well marked.

Spleen:-

Enlarged - fairly firm - soft almost diffluent in parts when cut. Contains chocolate coloured thick fluid inside. Does not show iron reaction.

Right Kidney:-

Small abscess in perirenal fat extending from under the capsule at lower extremity.

On section, numerous pyaemic abscesses are seen.

Capsule strips easily. Some chronic venous congestion and slight cirrhotic change.

Left Kidney:-

On section, shows a large abscess at apex of papilla.

No iron reaction in either kidney.

Suparenals healthy.

Haemolymph glands in front of lumbar vertebrae are large and numerous.

Stomach was not dilated. No haemorrhage into stomach or bowels.

Mucus membrane of stomach showed slight atrophy.
Intestinal mucus membrane healthy.
Brain and spinal cord were not examined.

Case 11.

Janet N., aet 34, single, domestic servant, was admitted on 2nd October 1906, complaining of shortness of breath and weakness. In December 1905 she began to feel weak and her feet and legs became swollen. She was then very short of breath on the least exertion. She was forced to give up her situation and she was admitted to Dunfermline Hospital in April 1906. She had an attack of sickness soon after being admitted to hospital which lasted two days. She has had occasional attacks of diarrhoea lasting for a few days at a time. Apart from these attacks she has had no abdominal pain. She was kept in Dunfermline Hospital for three months and the oedema had all gone from the feet and she felt much better when she left. She was kept on light diet and got some medicine but she does not know what it was. She gained seven pounds while in hospital. She then went to a convalescent home in the country for a month and while there she gained other seven pounds. She then returned to her home in August, and although she had not begun to do work she began to feel weak, and her feet began to swell. During the last few weeks she has had considerable pain across the stomach and bowels, and has been very short of breath. She has never had any haemorraghes.

Previously she had always been healthy and there is nothing of note in the family history.

On admission:-

Patient had a pale yellowish countenance with a certain amount of redness of the cheeks. Mucous membranes were pale. There was slight oedema of the feet.

Alimentary:-

Test meal frequently repeated invariably showed entire absence of free hydrochloric acid. Teeth were good _ tongue slightly furred. Appetite poor. Usually constipated. Stomach not dilated. Slight enlargement of liver. Spleen not enlarged. No tenderness or resistence in the abdomen.

Nervous:-

Occasional pains in arms and legs. No loss of power. Reflexes normal.

Urine:-

Acid 1026. does not give indican reaction. No abnormal constituents present.

Menstruation:-

Very irregular - the loss being always small.

Progress and Treatment:-

Patient was put on the usual treatment and as she was in hospital only three weeks before I left, the ultimate result cannot be recorded here. The blood counts for the three weeks showed a slight improvement and generally she had begun to feel better. She was put on the acid solution of arsenic and got up to 5 minims four times daily.

Blood Counts:-

2/10/06	R.B.C.	2,100,000	
	W.B.C.	4,800	L. 53% P. 46% E. 1%
	Hb.	45%	
	C.I.	1+	

9/10/06	R.B.C.	2,300,000	
	W.B.C.	5,200	L. 50% P. 48% B. 1% E. 1%
	Hb.	45%	
	C.I.	.9+	
16/10/06	R.B.C.	2,600,000	
	W.B.C.	6,000	L. 53% P. 45% B. 2%
	Hb.	50%	
	C.I.	.9+	
23/10/06	R.B.C.	2,500,000	
	W.B.C.	5,800	L. 59% P. 41%
	Hb.	50%	
	C.I.	1	

Films showed megaloblasts, megalocytes, poikilocytosis, polychromasia and relative lymphocytosis.

During the three weeks patient lost 2 lbs. in weight and she did not relish the farinaceous diet.

Case 12.

The following case is interesting because of its rarity. It appears to belong to that group of blood cases to which V. Leube attached the name Leukanaemia. Ewing[6] describes the typical symptoms of this condition to be as follows:- "Peracute or subacute course, fever, gingivitis and haemorrhages. Blood first shows the changes of pernicious anaemia with slight or no leucocytosis. Later, there is moderate or pronounced increase of large lymphocytes or myelocytes. There is moderate hperplasia of

spleen and lymph nodes"

In the present case the patient was a railway porter aet 59 who was admitted to Chalmers Hospital first on January 27th 1906 - complaining of pain in the left side, weakness and epistaxis. The history was that about the end of December 1905 he caught a chill which was next day followed by pain in the left side of the abdomen. He at once consulted his doctor who diagnosed pleurisy and ordered hot poultices to be applied. The pain was considerably relieved, but he felt very weak and remained in bed. On 16th January 1906 he had a severe epistaxis which lasted about three hours, and he had to have his nostrils plugged. The doctor again examined his side and found the spleen very much enlarged and so advised his removal to hospital.

Apart from having had smallpox thirty-two years ago, he had previously always been healthy.

Nothing of note in family history. Father and mother both dead - cause unknown.

On admission - patient was a well developed, fairly muscular man. Temperature was normal.

Mucous membranes were anaemic. Cheeks were somewhat high coloured. There was no dropsy. He complained of fairly constant cough and occasionally of palpitation, but there was no dyspnoca.

There was a soft mitral systolic bruit, but heart was not dilated. Pulse was regular, average 82. No arterio-sclerosis.

The blood flowed very freely - was watery and clotted with difficulty. Film showed irregular reds, no rouleaux formation, megaloblasts, normoblasts and megalocytes present. White corpuscles were also increased. There were no enlarged lymphatic glands. Thyroid was not enlarged. Spleen was very much enlarged and over the spleen during respiration, distinct friction could be felt and heard. Upper border of spleen was at level of 9th rib and the spleen extended one inch to right of midline at the level of the umbilicus and downwards for 2½" below the level of the umbilicus.

Progress and Treatment:-

Patient was kept at rest in bed and put on light diet. He had small doses of Fowler's solution increasing up to seven minims four times daily. His temperature remained practically normal throughout. He improved considerably and by 10th April he was able to leave hospital. He felt stronger and better but the condition of the spleen remained unchanged.

The following shows the condition of the blood:-

28/1/06	R.B.C.	2,600,000	
	W.B.C.	18,000	Polymorphs 48% Lymphocytes 47% Myelocytes 2.5% Basophils 2.5%
	Hb.	42%	
	C.I.	.8	
8/2/06	R.B.C.	2,500,000	
	W.B.C.	15,000	P. 45% L. 52% M. .5% B. 2%
	Hb.	40%	
	C.I.	.8	
19/2/06	R.B.C.	2,400,000	
	W.B.C.	14,800	P. 50% L. 47% M. .5% B. 2.5%
	Hb.	40%	
	C.I.	.8	
10/3/06	R.B.C.	2,940,000	
	W.B.C.	16,200	P. 48% L. 50% M. 1% B. 1%
	Hb.	45%	
	C.I.	.8	
20/3/06	R.B.C.	2,800,000	
	W.B.C.	15,500	P. 52% L. 46% M. 2%
	Hb.	43%	
	C.I.	.8	
1/4/06	R.B.C.	3,000,000	
	W.B.C.	18,000	P. 46% L. 51% M. 1% B. 2%
	Hb.	50%	
	C.I.	.8	
10/4/06	R.B.C.	3,200,000	
	W.B.C.	20,000	P. 49% L. 48% M. 1% B. 2%

10/4/06 Hb. 50%
C.I. .79

The films showed the same characters throughout, although latterly the megaloblasts and megalocytes were not quite so numerous. A few myelocytes were invariably present but never to any extent. After leaving hospital he was able to move about each day at home although he felt very weak. A month later he was able to go north to Sutherlandshire where he stayed for two months. During that time he felt very well and never had any more bleeding. He had a good appetite, and put on several pounds in weight. About the beginning of July he returned to Edinburgh, and soon afterwards he began to suffer from shortness of breath and a severe cough. He got gradually weaker and became unable to move about, and was again admitted to hospital on 1st October.

His condition was then very similar to that on previous admission. There were slight petechial haemorrhages on the back of both hands which he had noticed only for a few weeks. He had numerous bronchitic sounds over both lungs, and evidence of oedema of both bases. Spleen was slightly larger than before. Heart was not dilated.

A test meal was frequently given and in each ca

case showed an entire absence of free hydrochloric acid. His temperature remained between 99° and 100° F. A culture was taken from the blood and the report got from the Royal College of Physicians laboratory was that it gave a culture of a diplococcus. He was kept on the same treatment as formerly and when I saw him last he had remained fairly stationary He had no haemorrhages.

The following shows the condition of blood:-

1/10/06	R.B.C.	1,600,000	
	W.B.C.	7,000	P. 45% L. 51% M. 2% B. 2%
	Hb.	30%	
	C.I.	.9	
8/10/06	R.B.C.	1,500,000	
	W.B.C.	8,000	P. 48% L. 50% M. 1% B. 1%
	Hb.	30%	
	C.I.	1	
15/10/06	R.B.C	1,800,000	
	W.B.C.	10,000	P. 50% L. 47% M. 1.5% B. 1.5%
	Hb.	30%	
	C.I.	.8	
22/10/06	R.B.C.	2,000,000	
	W.B.C	10,500	P. 49% L. 50% M. 1%
	Hb.	35%	
	C.I.	.8	

Films showed a few megaloblasts, megalocytes and normoblasts. The leucocytosis was not so high as on former occasion but the relative proportion of the leucocytes remained practically the same.

From such an account of the case, all the signs and symptoms seemed to point to a mixture of pernicious anaemia with leucocythaemia. I have been unable to find any detailed account of the disease in any of the text books and as this present case when last I heard of him, was still alive, we had not the aid of postmortem evidence to guide us as to the nature of the disease.

Case 13.

Mrs. M, 34, Married, nullipara was admitted to Chalmers Hospital on 12th October 1906. In June 1906 she began to complain of pain after food which was usually relieved by vomiting . The vomiting was very persistent and occurred after almost every diet. The sickness lasted for about a month, although during that time she took practically nothing but milk. She had various medicines, but she gradually became weaker. During this time also she had great pain in legs and arms, and was unable to move the arms freely. The legs were not so much affected but she could not walk far because of the weakness.

She also became very short of breath on the least exertion. She had slight diarrhoea along with the sickness. Patient was seen by Dr. Gulland in end of August, and he diagnosed pernicious anaemia. Red Blood Corpuscles were then 1,500,000 and Haemoglobin 35%. She was put on small doses of arsenic and farinaceous diet. She began to improve rapidly on this treatment and for about a month before admission she had been able to walk about. She has slight pains in the legs and it was really because of these pains that she was admitted to hospital. She has had no sickness or abdominal discomfort lately.

There was nothing of note in previous health or in family history. On admission patient looked very healthy. There was nothing suggestive of pernicious anaemia in the countenance. Mucous membranes were slightly anaemic.

Test meal - showed entire absence of free hydrochloric acid. She had no dyspnoca - there was a soft mitral systolic murmur but heart was not dilated. She had slight tenderness over the calves. Knee jerks were present. There was no ankle clonus. Patient was kept on light diet and given 3 minims of acid arsenic after food. She was allowed to go about the ward and she had some faradism applied to the legs. She improved rapidly and in a few weeks

she was able to leave for home.

12/10/06	R.B.C.	3,000,000		
	W.B.C.	4,000	P.	42%
			L.	57%
			E.	1%
	Hb.	60%		
	C.I.	1		
19/10/06	R.B.C.	3,500,000		
	W.B.C.	5,200	P.	48%
			L.	52%
	Hb.	65%		
	C.I.	.9		
26/10/06	R.B.C.	3,600,000		
	W.B.C.	5,000	P.	49%
			L.	50%
			B.	1%
	Hb.	65%		
	C.I.	.9		

Case 14.

Mrs. M., aet 47 married 3 para, was admitted on 11th October 1906 complaining of sickness and diarrhoea. In May 1905 patient, who was then in Philadelphia, had a bad attack of sickness, vomiting and diarrhoea. About the same time she began to feel numbness in the hands, forearms, feet and legs. She was treated with strychnine and arsenic and kept on ordinary diet. She improved somewhat and was able to move about till October when she had a very severe attack of diarrhoea and sickness. She was very ill at this time and remained unconscious for three weeks. She was then seen by a specialist who examined the blood and diagnosed pernicious anaemia. He believed

that she had also an attack of dysentery - the motions being often as frequent as 40 per day and containing a fair amount of blood. There was very little pain with the diarrhoea. During this time she was fed on milk, champagne, whiskey and occasionally she had to have nutrient enemata. She was kept largely under the influence of morphia. She recovered remarkably well after this severe attack and was soon able to eat all sorts of foods. Soon afterwards phlebitis set in in both legs and she had again to lie up. Since then she has always had a great deal of pain in the legs when she walks about. She has had slight attacks of diarrhoea every now and again, since the last severe attack. After her recovery she was advised to come to this country and on the voyage she suffered considerably from diarrhoea. After landing here she did not improve and so she was advised to come to hospital.

She had previously been healthy and there was nothing of note in the family history.

On admission - patient had very white hair and a characteristic yellowish countenance.

Mucous membranes were very anaemic.

She had slight dyspnoca on exertion, and complained of general weakness. No murmurs were heard over the heart which was not dilated. A test meal

was given and the result showed an entire absence of free hydrochloric acid. Liver was slightly enlarged. Spleen not enlarged. There was no tenderness on palpating the abdomen.

She had considerable pain in the calves of the legs which were tender on pressure.

Plantar reflex caused flexion.

Urine showed well marked indican reaction, but contained no abnormal constituents.

Blood films showed megaloblasts, megalocytes and a few red cells showing granular degeneration. She had a slight evening rise of temperature for the first few days after admission but afterwards it settled down.

She was kept on farinaceous diet and given 3 minims of Fowler's solution four times daily. She was under observation only for a short time before I left hospital and although the blood had not begun to improve still she felt better, and had had practically no return of the diarrhoea or sickness. Faradism was applied daily to the legs, and the pains became much less marked.

11/10/06	R.B.C.	2,400,000	
	W.B.C.	5,200	L. 49% P. 50% B. 1%
	Hb.	50%	
	C.I.	1	

18/10/06	R.B.C.	2,200,000		
	W.B.C.	4,500	L.	50%
			P.	45%
			E.	1%
			B.	1%
	Hb.	50%		
	C.I.	1.29		
25/10/06	R.B.C.	2,500,000		
	W.B.C.	6,000	L.	51%
			P.	48%
			B.	1%
	Hb.	50%		
	C.I.	1		

Symptomatology.

By far the most constant and most important changes which can be recognised clinically during life are those which take place in the blood. The total quantity of blood in the body is very much reduced and frequently considerable difficulty is experienced in getting a drop large enough to fill the various pipettes required for examination. The coagulation of the blood is feebler than normal and in case 9 especially in the later stages, I had the greatest difficulty in arresting the oozing from the pricks in the ear from which I obtained blood for examination. On the last two occasions on which the blood was examined, the oozing continued for about 8 hours in spite of the application of all the usual styptic remedies. The colour of the blood is usually slightly paler than normal and in the later stages

it becomes extremely pale and watery.

Hayem[19] found the coagulability of the blood in pernicious anaemia normal, but Ehrlich and Grawitz report great difficulty in many cases in arresting the oozing from pricks. The specific gravity of the blood is constantly reduced, but from the series of tables drawn up by Dieballa there appears to be no close relationship between the specific gravity and the number of Red Blood Corpuscles.

Haemoglobin:-

The percentage of Haemoglobin is invariably reduced although the reduction may vary within wide limits. It is not as a rule so low as in secondary anaemias of equal severity. The reduction in the haemoglobin is usually coincident with increased severity in the general symptoms, but there are exceptions, and Ehrlich and Lazarus[1] report cases with marked morphological changes and severe general symptoms where the haemoglobin averaged 60 to 70%.

Red Blood Corpuscles:-

are invariably reduced. The counts depend largely on the stage at which the disease is seen, and it is a general rule that the more marked the diminution in Red Blood Corpuscles

the more severe is the case. Ewing[6] makes the general statement that life is seldom prolonged when the reds fall below 400,000 while many patients die before the reduction in the red corpuscles becomes so pronounced.

In two of the foregoing cases which proved fatal the red cells numbered 700,000 shortly before death while in the other fatal case which was evidently due to a complication, the red cells numbered 2,000,000 on the day of the patient's death.

The different varieties of red cells found in this disease are important.

Megalocytes or large red blood corpuscles containing a large quantity of haemoglobin are numerous in the blood. The average size of these cells is from 11 to 13 m. Ewing[6] states that these cells must form 33% of the red corpuscles, otherwise the diagnosis of pernicious anaemia is doubtful.

They usually increase with the severity of the disease.

Microcytes, or abnormally small red cells may also be present especially in advanced cases, but they have not the same diagnostic value.

Poikilocytosis or deformed red cells are

usually numerous as in all severe anaemias.

Megaloblasts or large nucleated red cells are said by all writers to occur in the blood. In practically every case a few megaloblasts may be seen, although in less severe cases several films may have to be searched before one can be found. As a general rule the more severe the case the more megaloblasts will be found in the blood. Cases of aplastic pernicious anaemia such as case 9, are practically, so far as is known, the only exception in which megaloblasts are not found in the blood, and these must not be lost sight of when the question of diagnosis is being considered.

Normoblasts or small neucleated red cells, are usually also present in the blood but they have not the same diagnostic value since they may be found also in secondary anaemia. In pernicious anaemia they are not as a rule so numerous as the megaloblasts, and in the preceding cases I have found them only very occasionally present.

Dorn, in a paper read at Berlin in 1891, regafds an increase of normoblasts as a favourable sign, and reports a case where the symptoms improved marked ly

improved markedly coincident with a large increase of normoblasts in the blood.

This observation has not been confirmed by other writers and I have found the normoblasts of no value whatever as regards prognosis.

Degenerative changes in the red cells:-

Polychromatophilia is usually well seen especially in the megaloblasts but this may also occur in severe secondary anaemia.

Punctate basophilia is said to be fairly frequent especially in the megaloblasts and megalocytes.

I have observed it in four of the cases and it usually was pronounced in all the films taken at various times. As far as my observation goes, it has been almost invariably present in the megalocytes but many writers state that it is most commonly found in megaloblasts.

Lazarus states that punctate basophilia in the reds is persistent in pernicious anaemia, and I have found it present in practically every film of those four cases, but I could not detect any relation between the number of cells showing this degeneration and the general severity of the disease. The absence of rouleaux in fresh films is almost invariably well marked.

Colour Index:-

Much more important than either the amount of haemoglobin, or the number of red corpuscles, is the relation between the two- the so called colour index of the blood. The colour index in pernicious anaemia is always high - in many cases

greater than unity and this is one of the most important points in differentiating pernicious anaemia. The high colour index is due to the fact that although the red blood corpuscles are so markedly reduced, yet each individual cell contains more than the average amount of haemoglobin. The colour index on the whole serves as a fairly good guide in estimating the progress of a case. Especially does this seem to be so, judging from the foregoing cases, in those cases which deteriorate where the colour index correspondingly rises, but on the other hand the colour index does not appear to fall correspondingly low in those cases, which in all other respects, are evidently improving.

Cabot and Bramwell[2] give the average colour index in chlorosis and secondary anaemia as about .5 while in perhicious anaemia it is usually normal or slightly above normal, and almost never approaches such a low figure as .5. Ehrlich calls attention to a few exceptional cases of pernicious anaemia where the colour index may be very low.

White Blood Corpuscles:-

Much less attention has been paid to the leucocytes in pernicious anaemia than to the other

constituents of the blood. This is probably due to the fact that little can be learned from them, either as regards diagnosis or prognosis. As an almost invariable rule, the leucocytes are diminished in this disease as is well seen from the tables of the foregoing cases, and when they are increased as they were for a short time in cases 6 and 9, then the leucocytosis may be taken to denote some complication. The presence of leucocytosis may thus be of value in the diagnosis of a complication arising during the course of pernicious anaemia. The irregular pyrexias, which are so common in this disease, always make one suspicious that there may be something definite to account for them, but in many cases nothing can be detected, and these pyrexias appear to be but a symptom of the disease. I have repeatedly examined for leucocytosis during these pyrexias where no definite complication could be detected, and I have never found any marked increase in the leucocytes. On the other hand very severe complications such as the pyaemia which occurred in case 10 may not cause leucocytosis, but it is well known that any severe toxic condition which is likely to prove fatal is not accompanied by leucocytosis. Most writers state that there is

slight increase in the leucocytes just previous to death but in the three fatal cases recorded in this increase was only very slight.

From inspection of the differential counts made, the most striking fact is the large percentage of lymphocytes present and the relative diminution in the polymorphonuclear leucocytes. This result agrees with that recorded by Ehrlich and other writers, and differs from that of MacCrae who found in 30 cases an average of 64% polymorphs, and 34% lymphocytes. In the leucocytosis of complications it appears to be unusual to find such a high percentage of polymorphs as were present in both of these cases. Geissler[20] reports a case where there was marked leucocytosis and the lymphocytes numbered 90%. Grawitz[12] reports another case where the myelocytes numbered 20%. Such cases with large increase of lymphocytes or myelocytes are apt to be mistaken for cases of leucocythaemia.

The eosinophiles vary within slight limits, and no great importance can be attached to them as regards prognosis. They are usually reduced in number to a slight extent. Myelocytes were present in three of the cases to a slight extent on several occasions on which the blood was examined.

Subjective Symptoms.

In the great majority of the cases which I have recorded the predominant symptom complained of was "General Weakness" which had gradually compelled the patient to give up work. This symptom is found to be very generally present in most cases of pernicious anaemia, and may often be the only thing complained of, so that many cases of pernicious anaemia go undetected, being treated as ordinary anaemias or general debility. A study of the history in the above cases will serve to show how variable the symptoms are, and how in one case, one set of symptoms will predominate, while in another the leading symptoms are entirely different. Gulland[21] classifies the symptoms of pernicious anaemia into three great groups:-

(1) Symptoms referable to affections of blood and circulation.

(2) Symptoms referable to gastrointestinal system.

(3) Symptoms referable to nervous system.

The pallor of the skin is in most cases very characteristic so that the experienced eye can recognise the disease in many cases from the countenance of the patient. The colour is usually described as lemon yellow and is quite different from the pallor

of chlorosis or cachexia. In many cases there is a peculiar apathetic expression on the face. Oedema is common about the eyelids and feet, and it was present in all the severe cases mentioned above, especially about the ankles. Small haemorrhages into the skin and mucous membranes are reported to be fairly frequent but large haemorrhages are rare. Very severe haemorrhage from the nose occurred on three occasions in case 7. Small haemorrhages were present in three of my cases, and two of these proved fatal, while the third was case 12 which cannot regarded as a case of pure pernicious anaemia.

Urine:-

There are no characteristic changes found in the urine. I have practically always found a well marked indican reaction present in all the urines, and at every stage of the disease. This is usually got in gastrointestinal disorders, and it is not special to pernicious anaemia. Schaumann declares that the indican reaction is practically constant, but other writers are inclined to believe that it is variable, and may often be absent. Laache[22] reports a case where blood was found in the urine, but I have not been able to find another such case recorded in the

literature. Albumen has been found in traces but never constantly present in a case of pernicious anaemia. Sugar has never been reported to be present in a case of pernicious anaemia.

Uric acid has occasionally been found increased, and in case 9 the urine on several occasions showed very numerous crystals of uric acid.

Acetone has been found by Van Jaksch in one case, but nothing is known as to its significance in this connection.

The general nutrition of the patient is usually well maintained till an advanced stage of the disease is reached. The subcutaneous fat is usually found remarkably well developed in cases which terminate fatally, and the muscles do not as a rule showed marked wasting, although they are often exceedingly flabby and seem to have lost all tone. The patient's weight is usually fairly well maintained and even in those of the above cases which terminated fatally there was a loss of only a few pounds from the date of admission till the date of death. Considerable loss of weight will often be found to follow severe gastrointestinal symptoms especially vomiting and diarrhoea.

The temperature curve in pernicious anaemia is

very variable and nothing definite can be deduced from a study of different charts. An irregular pyrexia is commonly present, but as a general rule this tends to settle down as the case improves, although in most of the cases every now and then, the temperature may suddenly rise when nothing can be found to account for it. As already mentioned, these pyrexias are not accompanied by leucocytosis, unless due to some complication.

Many patients complain of symptoms referable to the heart, such as palpitation, praecordial pain and dyspnoea, but in none of the above cases have these been the first symptoms complained of, nor have they ever been extremely marked except in the very advanced cases. Examination of the heart in most cases reveals the presence of systolic bruits at one or other of the valvular areas. These, I have invariably found associated with a regular pulse and practically no cardiac dilation, so that it is allowable to assume that they are in most cases purely functional. IN only one case was there a presystolic murmur heard at the mitral area, and in this case there were no signs of failure of compensation. The systolic murmurs, I have found most commonly present at the mitral and pulmonary area, and only very rarely at the aortic or tricuspid.

Alimentary System:-

Several writers have reported cases of extreme hyperaesthesia of the tongue and mucous membrane of the mouth especially in cases where there was excoriation or ulceration of the tongue. This symptom was not present in any of the above cases and in case 10 the excoriations on the tongue and tonsils caused him no inconvenience.

Gastric symptoms have been present in a more or less marked degree in almost every one of the cases. The common complaint was an indefinite pain or uneasiness across the abdomen with occasional attacks of diarrhoea. Vomiting has been extremely rare while patients have been under treatment in hospital, although it was frequently a symptom previous to admission.

Recently, attention has been directed to chemical examination of the gastric juice in cases of pernicious anaemia. Schaumann and Martius[23] found the hydrochloric acid diminished or even absent in 10 out of 11 cases. Einhorn, on the other hand states that he has found as a general rule no appreciable diminution of hydrochloric acid. Test meals were repeatedly given in ten of the above cases and the following shows the average amount of free hydrochloric acid

present in each case:-

Case 5.	.1 H.Cl.
Case 6.	.12 H.Cl.
Case 7.	absent
Case 8.	absent
Case 9.	.116 H.Cl.
Case 10.	.16 H.Cl.
Case 11.	absent
Case 12.	absent
Case 13.	absent
Case 14.	absent.

From these statistics it will be seen that the hydrochloric acid was invariably diminished, and in six of the cases it was entirely absent. The amount of acid present does not appear to have any direct relation to the severity of the symptoms or of the blood changes, and in case 13 which was the least severe of the series, the free acid was entirely absent. No organic acids were found on any occasion. Constipation or Diarrhoea may be present but under treatment these are seldom prominent symptoms. In case 6 there was very marked abdominal distention but the abdomen was never rigid and hard and it was not associated with constipation. The faeces were frequently examined, especially with the view of ascertaining the presence of ova, but they never presented anything characteristic. In a few of the cases the liver was slightly

enlarged and in one case it was tender on pressure. The spleen was found slightly enlarged in only one case.

Nervous Symptoms:-

There is often a marked indifference to th things in general. This was seen to a slight extent in several of the cases, but was extremely marked in case 9 where the patient's one desire appeared to be left alone . She took very little interest in the visits of her friends, but the indifference in this case may have been partly due to the extreme weakness. Mania and melancholia have been described as occurring in a few rare cases of pernicious anaemia. Marcus[24] reports a case which recovered where there were marked delusions of granduer. Pickett[25] sums up the mental condition which is occasionally found in pernicious anaemia as follows:- "A composite picture of the mental disturbances in these cases presents a shallow confusion with impairment of ideas in time and place, more marked on waking from sleep. Illusions particularly of identity are common. Hallucinations, at times pertaining to any of

the senses: Delusions may arise but are usually transient though they may persist for considerable periods."

In only one of the above cases - case 10 - were there any cerebral symptoms, and as will be seen from the account given of the case, the symptoms agree in the main with Pickett's description. Emotionalism was marked in two cases. Clinical symptoms referable to the spinal cord and peripheral nerves are common. In many of the cases, the nervous symptoms present do not conform accurately to the symptoms of any of the recognised lesions of the spinal cord. In several of the cases the symptoms appeared to be due to peripheral neuritis. In case 4 the symptoms of periphal neuritis were well marked, but they can hardly account for the cerebral condition. In case 7 the patient presented practically a complete picture of tabes, except for the important omission of the Argyll Robertson phenomenon. In case 9 shortly before death the plantar reflex caused extension and the knee jerks were exaggerated, but this might be accounted for by a haemorrhage into the lateral column of the cord. In several cases there was loss of knee jerks without any other sign

of involvment of the nervous system.
Leichtenstein in 1883 first described two cases of pernicious anaemia with symptoms of tabes. The nervous symptoms usually resemble most closely those of tabes but in several cases the symptoms are those of spastic paralysis. Von Wort[26] reports a case where the symptoms were those of disseminated sclerosisl and several similar cases are reported in the journal of the American Medical Association, March 1901.
Henry[27] reports a case of wrist drop from peripheral neuritis. The nueritis in some cases appears to be due to the arsenic but in many cases it is present before arsenic has been given. Billings[28] believes that these nervous symptoms are due to the action of a toxin (probably gastrointestinal in origin) which tends to produce sclerosis of the spinal cord. The nervous symptoms do not always correspond to the severity of the blood changes although in the majority of cases they are influenced by the general condition of the patient. Nonne[29] reports a case where the tabetic symptoms slowly improved while the blood gradually became worse and the patient eventually died.
Bowman[30] on the other hand reports a case where

under arsenic both the nervous symptoms and the blood changes showed improvment for a time, and eventually when the patient had a relapse both again became marked. The association of pernicious anaemia with nervous symptoms is a very remarkable one, and although definite anatomical lesions have accasionally been found postmortem, still in many cases the symptoms and the lesions found postmortem do not correspond. In some recorded cases the nervous symptoms have been noted first, while most usually they appear later in the disease.

Some authors report nervous symptoms in as many as 40% of cases of pernicious anaemia.

Mac Rae[31] found nervous symptoms in 20 out of 50 cases. The symptoms varied from only slight anaesthesia to complete paraplegia with loss of control of bladder and rectum. All those cases which proved fatal showed involvment of posterior columns, and a few showed also involvment of latreal columns. The changes were found chiefly in the cervical region. He found that the symptoms improved with the improvement of the blood and therefore he believed that the symptoms were due to the anaemia. Billings[32] reports a well marked

relation between diffuse cord degeneration and pernicious anaemia. He believes it highly probable that haemolysis and the cord changes are due to the same toxin.

PATHOLOGY.

The changes which are found postmortem in pernicious anaemia are fairly constant. The following is a summary of the changes found by Gulland and Goodall[33] after a study of 17 cases and these may be taken as typical of the changes in general.

ALIMENTARY.

No change in tongue.

Stomach and Intestines:-

All showed some atrophy which in many cases appeared to be a postmortem change. One case showed ulceration of stomach. No iron was found. There were colonies of organisms in two cases.

Liver:-

Fatty in every case.

Iron reaction present - best marked in the most acute cases. Necrotic looking areas were found in the middle zone of the lobules and

See page 91.

these were better marked in the chronic cases.

Spleen:-

Contained some pigment some of which gave iron reaction.

Kidneys:-

Showed chronic or interstitial nephritis. In 10 cases they gave the iron reaction.

Haemolymph Glands:-

Showed marked haemolytic changes in nearly every case. Small amount of pigment. Slight iron reaction.

Bone Marrow:-

Always hypertrophied and dark red. Megaloblasts were most numerous in the marrow when they had been found to be most numerous in the blood.

The changes found postmortem in case 8 may be regarded as practically typical of pernicious anaemia. The question of atrophy of the stomach and intestinal mucous membrane is one which is much disputed. Some authorities believe that the atrophy is purely a postmortem change and in the two cases above where formalin was injected and in the third case which was examined soon after death there was very little atrophy, although some parts of the alimentary canal even then did show it. It would appear then that atrophy

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does very often take place but in many cases it is exaggerated by postmortem change. In case 10 the changes were modified by death being ultimately due to pyaemia but the essential changes of pernicious anaemia were also present. In case 9 the striking point was the almost complete degeneration of the marrow into fat. From the clinical symptoms and the other characteristic pathological changes present in this case, I think there can be little doubt that the case must be classed as one of pernicious anaemia. The view which finds most favour at present is that pernicious anaemia is due to a toxin produced in some part of the body which acts directly on the bone marrow interfering with normoblastic blood formation, leading to megaloblastic formation and acting with negative chemiotaxis upon lencocytes especially of the neutrophile variety. On that hypothesis case 9 might be explained by the greater degree of severity of the toxin. From the few cases which have been recorded, it seems permissible to state that such cases all run a rapid course. This fact also coincides with the view that the toxin may in these cases be more virulent. Again, it is a well known fact that a toxin may produce different results on the leucocytes according to the degree of its virulence. Thus, in an ordinary case of pneumonia we find the leucocytes very

considerably increased, while in a very severe case which ultimately proves fatal, they are usually not increased and may even be below normal. In the case reported by Muir, he believes the condition of the marrow to be primary, but on this hypothesis he requires to explain the other symptoms as being due to some intercurrent condition. Primary fatty degeneration is rare, and the fact of the other organs being also fatty seems to point to some toxic cause. The cases of aplastic pernicious anaemia recorded, are as yet so rare that as Ewing suggests, it may be premature to draw from such cases, conclusions regarding the pathological anatomy and pathogenesis of true pernicious anaemia.

Gulland and Goodall sum up their views as to the pathogenesis of pernicious anaemia thus. "There is no direct evidence of special disease of the intestine and the intestine need not be the primary seat of toxin production, although in some cases it probably is. In some part of the body a toxin is produced which acts directly on the bone marrow. It is possible that certain individuals from congenital defect in the marrow may be specially prone to the disease as there is little doubt that the megaloblastic degeneration represents a reversion to the

foetal type."

Strauss[34] after a study of 10 cases comes to the conclusion that there is no relationship between pernicious anaemia and gasterointestinal disease.

DIAGNOSIS.

The general appearance of the patient may often suggest a diagnosis or at least cause one to examine the blood, which after all is the only sure guide to an absolute diagnosis. In a typical case the following characteristics are usually present in the blood.

(1) High Colour Index. (2) Megaloblasts.
(3) Megalocytes. (4) Leucopenia with relative lymphocytosis.
(5) Polychromatophilia and other degenerations of the red cells.

In the earlier stages of the disease we may not find such a characteristic picture in the blood, and then it becomes ~~it becomes~~ important to know the relative value of these changes individually, and to find whether any is pathognomonic of the disease.

The presence of a high colour index is one of the best indications of pernicious anaemia. In chlorosis and in secondary anaemia the index is always considerably below 1 while in pernicious anaemia it approaches, equals, or often exceeds unity. The absence of a high colour index then should make one hesitate to

pronounce a diagnosis of pernicious anaemia. But the presence of a high colour index cannot be regarded as pathognomomic of the disease since it has been found, though rarely, in other diseases.

Emery[36] reports a case of gastric cancer with 4,000,000 red cells and a colour index of1.15. In this case there was a polymorphic leucocytosis which helped to distinguish it from pernicious anaemia. He reports also 3 cases of purpura haemorrhagica with high colour index, although it is usual in that disease to find a low colour index.

Webb[37] considers the presence of megaloblasts along with a high colour index as practically pathognomonic. He also reports a case of Raynaud's disease with high colour index, but no megaloblasts. Megaloblasts are present at one time or another in practically all cases of pernicious anaemia, although failure to find them is not of great importance as evidence against the disease. There appears to be considerable difference of opinion regarding the diagnostic value of the megaloblast. Hunter[38] states that the presence of megaloblasts are not characteristic of pernicious anaemia, while Goodall[39] states that megaloblasts are extremely rare in any other disease than pernicious anaemia, and never

more numerous than normoblasts. Gulland and Goodall[33] state that the essential feature of pernicious anaemia, and the criterion in its diagnosis is that it is a megaloblastic anaemia. Megaloblasts should not be considered absent after examination of one film, but several films should be searched before pronouncing an opinion. Emery[36] states that he has never found megaloblasts in a case where the red count reached over 3,000,000 and rarely when the count was between 2 and 3 millions. I cannot quite agree with this statement, although as a general rule the megaloblasts become fewer as the red count increases. For that reason the high colour index is most important in the diagnosis of slight cases, as I have never found it fall much below 1 even in those cases which have made the most satisfactory progress.

The presence of megaloblasts, although an important diagnostic sign is not in itself pathognomomic since they have been described as occurring in other conditions. Thus Houston[39] reports a case of mammary cancer with high colour index and megaloblasts, in which postmortem there were found numerous secondary nodules in the bone marrow.

Megaloblasts have also been described as occurring in infantile anaemia (Von Jaksch's anaemia).

Ehrlich states that the occurrence of normoblasts carries no weight in the diagnosis. He believes that they are less numerous than the megaloblasts. Cabot[2] found in 139 examinations that normoblasts were always present if megaloblasts were present and Coles[2] found that in the early stages of the disease the normoblasts may predominate. Lazarus[19] on the other hand considers their simultaneous occurrence as a rarity. In all the films from the above cases I have found normoblasts exceedingly rare and in most of the cases they were absent from the films on every occasion. The cases of aplastic pernicious anaemia are as yet so rare that it would be unwise to depart from the general rule that megaloblasts are essential to the diagnosis in pernicious anaemia. At the same time when one finds all the symptoms of pernicious anaemia along with a low red count and a high colour index and absence of megaloblasts and megalocytes, one must not forget the possibility of this rare form of the disease.

The presence of megalocytes is perhaps more important in diagnosis since they are usually more constantly present than megaloblasts. Ewing[6] states that to diagnose pernicious anaemia megalocytes should form at least 33% of the red cells. Megalocytes are

well known to occur in icterus, and I have seen them in quite a considerable number in two cases of icterus which were under treatment in the ward, but the blood had none of the other characteristics of pernicious anaemia. Microcytes may be found in any anaemia and are of no value from a diagnostic point of view. It may be difficult to draw an accurate dividing line between a normal sized red cell and a megalocyte, but for ordinary clinical purposes the megalocytes may be recognised by comparison with a normal blood film or by using the squares of a Thomas Zeiss counting chamber. The lines intersecting the double ruled squares are 25m from the edges. The average size of a red blood corpuscle is just over 8m (1/3 the distance): the average size of a megalocyte is 12m (½ the distance).

The Leucopenia is well marked in pernicious anaemia and this helps to distinguish it from secondary anaemias. Leucocytosis, if present, is against the diagnosis of pernicious anaemia and if it occurs in an undoubted case of pernicious anaemia then it almost invariably denotes some complication. No one change in the blood can be regarded as pathognomomic of pernicious anaemia but the presence of megaloblasts, megalocytes and high colour index together form a picture

such as we get in practically no other disease.

In hospital practice, where the blood is examined as a routine in practically every medical case, cases of pernicious anaemia are not likely to be missed, but in general practice the diagnosis of anaemia or general debility is often attached to what really turns out to be pernicious anaemia. The explanation is of course not far to seek. Examination of the blood has not yet come to be looked upon as a routine practice, but it affords such a useful guide in the diagnosis of many obscure cases that it seems almost inexcusable for anyone to dispense with its aid.

The examination of a stained film will in most cases be sufficient to give one a good idea, although when possible it is much more satisfactory to have an actual count made.

A concealed gastric carcinoma may produce symptoms practically similar to those of pernicious anaemia, but in the former case the blood shows the characteristics of a secondary anaemia. In a few rare cases the two diseases seem to coexist and as a rule, the one or other is discovered only at the postmortem. Some advanced cases of pernicious anaemia have been mistaken for typhoid or meningitis of an irregular type.

The predominance of symptoms belonging to one or other of the three systems usually affected is apt to put one off the track, and if the blood be not examined and a correct diagnosis made, the result is that instead of treating the disease one finds oneself simply treating symptoms with usually unfortunate results.

PROGNOSIS.

Gulland[21] divides cases of pernicious anaemia into three classes - acute, subacute or relapsing, and chronic, but he states that unfortunately it is impossible to diagnose with certainty, even from a careful examination of the blood, to which class any particular case belongs. Those cases of aplastic pernicious anaemia, such as case 9 seem to be extremely rapid in their course and inevitably reach a fatal termination without any attempt at recovery. In this case the patient was able for her usual duties till within six weeks of her death, and the cases of Pasteur and Muir already quoted also ran a rapid course lasting only a few weeks. The usual history in the majority of cases treated in hospital is that they recover very considerably up to a certain extent. The general symptoms improve along

with the improvement in the blood, and the patient is usually able to leave hospital feeling much better. The following table shows the state of the blood in six patients on the day of their dismissal from hospital.

Case 2.	R.B.C.	3,470,000
	Hb.	65%
	C.I.	.9
Case 3.	R.B.C.	3,140,000
	Hb.	70%
	C.I.	1.1
Case 4.	R.B.C.	3,210,000
	Hb.	65%
	C.I.	1+
Case 5.	R.B.C.	3,840,000
	Hb.	65%
	C.I.	.8
Case 6.	R.B.C.	4,000,000
	Hb.	85%
	C.I.	1+
Case 7.	R.B.C.	3,400,000
	Hb.	55%
	C.I.	.8

These counts, on the whole, indicate fairly well the result of treatment. Improvement is found to take place up to a certain extent and I have usually found it impossible to get the red cells higher than between three and four million, although many cases leave hospital before the acme of improvement has been reached, and they might, no doubt, improve further under treatment. The colour index remains high and the haemoglobin often reaches as high as 75 to 80%.

Unfortunately however, the improvement seems to be in most cases temporary, and relapses are the rule. How far these may be due to want of arsenic, to return to hard work, or to want of supervisionregarding diet it is impossible to say, but such a thing as an absolute cure of pernicious anaemia is practically unknown. Improvement may suddenly begin to take place even in a very severe case apparently independently of treatment and this is specially seen after what has been described as gastric crises. In case 8, for several weeks there was no improvement in the blood or in the general symptoms - patient complaining greatly of pain in the stomach. The stomach was then washed out daily, and he was given hydrochloric acid after food, and from that time he steadily began to improve. Naturally the improvement was attributed to the treatment of the gastric symptoms, but it may have occurred quite independently. Cases which do not begin to show some improvement after a few weeks active treatment seem less likly to do well, although there appears to be almost nothing distinctive on which to found a prognosis for any individual case. The more profound the blood changes, as a rule, the less favourable must be the prognosis. Yet Quincke records a case where the red corpuscles had fallen to 143,000 and yet the patient recovered. A large

number of megaloblasts and megalocytes with very marked diminution of haemoglobin is ~~one~~ of grave omen. Luyt regarded the mitotic division of the nuclei of megaloblasts as of grave prognosis, but such nuclei have been observed in two of the above cases, and both of these recovered sufficently to leave hospital feeling much better. Dock[40] states that we are not justified in ascribing to mitosis in the circulating erythroblasts any diagnostic or prognostic value. The duration of the disease is also very variable and the more one collects statistics in regard to this, the more confusing do they appear to become.

Sandoz reports a case which proved fatal in fourteen days while some patients have been under competent observation with this disease for eighteen years, having occasional relapses every now and then. Authorities seem to fix the limit of five years arbitrarily, and if the patient has no remission after that time, they regard the case as a cure, but many of the cases of so called cures must be regarded either as Bothriocephalus Latus anaemias or secondary anaemias, and Ehrlich has no hesitation in pronouncing the disease incurable. Even in the short time that I have had the opportunity of observing the above cases several of them have returned as out-patients complaining of some of the old symptoms and two were readmitt-

ed for the second time within six months.

Gulland[21] regards the onset of coma when not due to intercurrent disease as an extremely grave omen, and he had seen only one such case recover. Laache[22] reports a case which was comatose for five days and then roused up and gradually improved, and from the history given by cases four and thirteen, they both appear to have had coma for a considerable time, and yet they recovered.

COMPLICATIONS.

Complications in pernicious anaemia are exceedingly rare. Any intercurrent disease may of course occur as it would in an ordinary patient, but pernicious anaemia does not appear to predispose specially to other diseased conditions.

Thrombosis:

> Thrombosis is rare in pernicious anaemia as compared with other anaemias - the explanation usually being the diminished coagulability of the blood in pernicious anaemia. It did not occur in any of the above cases while in hospital, but in case 13 there was a definite history of it having occured previous to admission.

Gangrene:

> The gangrene which occurred in case 8 is more commonly seen in cases of acute lymphatic leukaemia. In the only two cases which I have seen of this disease both developed spreading gangrene in the mouth which rapidly proved fatal, and I

was much surprised to find that the gangrene in case 8 did not go on spreading, but on the contrary completely healed.

Traces of albumen are occasionally found in the urine and Laache[22] has reported two cases where there was postmortem evidence of nephritis. Several cases have been reported in which suppurative foci were found all over the body and Laache reports a case where there were multiple abscesses in the skin. Case 10 developed pyaemia before death, and postmortem pyaemic abscesses were found in most of the internal organs. Gay[41] reports a fatal case of pernicious anaemia with gastroptosis and enteroptosis, but this case appears to be more a coincidence than a complication.

TREATMENT.

Since the actual cause of this disease has not yet been discovered no treatment directed against any of the various supposed causes has proved very beneficial, and unfortunately there is no actual specific remedy known for the disease. Those cases which are due to the Bothriocephalus Latus can be cured by the removal of the worm which is usually effected by ordinary doses of liquid extract of male fern, and as this treatment is followed by no ill effects, some

authorities recommend that it showed be tried, even where there is a negative history. Since the alimentary canal plays such a part in the symptomatology of most cases, naturally it has attracted considerable attention in regard to treatment. Hunter lays down the following rules for treatment:

(1) Antisepsis of the mouth.
(2) Gastrointestinal antisepsis.
(3) Arsenic.
(4) Antistreptococcal serum.

The chief drug employed as an intestinal antiseptic has been salol, and Dieballa[42] ascribes complete cure in one case to the use of salol after failure with all other methods of treatment. On account of the practical impossibility of disinfecting the intestinal canal, it seems difficult to understand why improvement should follow the use of salol acting as an antiseptic, and the improvement is much more likely to be a coincidence than a result. Salol was tried extensively in case 10 when the gastrointestinal symptoms were most marked, but like the other modes of treatment in this case, it was followed by no improvement. It was tried also in two other cases but no result could be attributed to it. In case 10 the small abrasions on the tongue and tonsils were touched with pure carbolic acid, and the mouth was washed out frequently till these healed, but as a routine practice

unless there were any local indications for it, no special treatment was applied by way of rendering the mouth antiseptic. Attention to the stomach and bowels is most important. Sandoz[9], as already stated, claims to have cured a case by repeated gastric lavage. This was also tried frequently in several of the foregoing cases and in case 9 improvement appeared to date from the beginning of this treatment, but in the other cases there was no such fortunate result.

As a routine treatment, every case in hospital had a saline enema each morning so that the lower bowel was well irrigated and constipation prevented.

As regards the administration of antistreptococceal serum in this disease I have had no experience, but although it has been strongly recommended by Hunter, yet the almost universal opinion of those who have tried it is that the results are disappointing and do not justify its use. Organotherapy has also been tried in pernicious anaemia. Bonemarrow has been administered by several investigators including Fraser, Grawitz and others. The results are somewhat conflicting - several having noted improvements after its administration, while Grawitz, notably, states that it had absolutely no effect. In many cases it was given along with arsenic so that it is difficult

to attribute the result to it alone. Recently John Brunton[43] reports a case which improved greatly on bone marrow when she seemed to be in a hopeless condition and had already had arsenic. It was administered first in the fresh state and latterly as tablets. In only two of the above cases was bone marrow tried, but so far as one could judge the result was not encouraging.

The treatment by transfusion was formerly given an extended trial but repeated failure has caused it to be practically abandoned. The intravenous injection of blood or saline is now used, if at all, only in severe cases with coma or collapse, and even then the improvement when it does occur, may occur independently of the treatment. In case 8 saline was injected intravenously in the last stage of the disease but apart from improving the pulse for a very short time it produced no appreciable result.

Of drugs which have been used in the treatment of pernicicus anaemia all authorities are agreed that the best results are obtained from the use of arsenic. This was first recommended by Byrom Bramwell in 1877 and although it cannot be regarded as a specific, since it cannot cure the condition, still it is so far a specific that no other drug can replace it. Battman has shown that arsenic in large doses stimu-

lates the bone marrow which causes young elements of greater resisting power to be thrown into the circulation, while it also to a less extent destroys the corpuscles already found in the blood. The arsenic is usually administered in liquid form as Fowler's solution and it is given in increasingly large doses stopping short of toxic symptoms. The arsenic is apt to aggravate any existing gastric disturbance and it should be administered after meals and may be given along with sodium bicarbonate. I have not been able to get up to very large doses in any of the cases, as with about 10 minims four times daily toxic symptoms usually began to show themselves. The toxic symptoms of arsenic especially the gastric disturbance and the neuritis, are almost identical with the symptoms of pernicious anaemia and it may be difficult to differentiate them, but if symptoms appear after large doses of arsenic which were previously absent, then one may assume that these are due to the arsenic, and the dose should be reduced. The fairly constant diminution of hydrochloric acid in the gastric juice suggests treatment by administration of hydrochloric acid after food and this was carried out in several of the cases - twenty minims of acid hydrochloric dilut. being given every ten minutes after a meal for three doses. In a few cases the acid

preparation of arsenic was substituted for Fowler's solution. The acid in some cases caused the patients to feel more comfortable but no marked improvement could be credited to it.

Formerly, iron, quinine and general tonics were largely given in pernicious anaemia, but the post-mortem excess of iron which is found in the internal organs would seem to contraindicate the administration of this drug.

The question of diet is one of great importance. Some authorities treat pernicious anaemia by strong nourishing diet while others lay great stress on restricted diet. Of the former treatment I have no experience whatever, as to have put any of the above patients on such a diet would have been regarded as an unjustifiable experiment. The only evidence against this treatment which can therefore be got from the above cases is to be obtained from the history previous to admission. In many of the cases before admission sickness, vomiting and diarrhoea were prominent symptoms while it is noteworthy that after admission these symptoms very largely disappeared and in practically no case did they persist. Chemical examination of the gastric contents is also in favour of the latter line of treatment. As a

routine treatment patients were put on light diet while the very worst cases were kept on farinaceous diet. In no case at any stage of the disease was meat allowed. By a glance at the tables of weights one would naturally suggest that these are not a strong argument in favour of the light diet as in none of the cases was there marked increse in weight. The three cases which were readmitted a second time had each put on nearly a stone after leaving hospital and before they began to relapse, but several reasons may be adduced to account for this. In the first place, according to the patient's own statements, they had obeyed orders and had lived on light diet all the time so that the increase cannot be put down to the different diet. The great improvement in the body weight after leaving hospital seems to show that the weight begins to increase much more rapidly after the symptoms have disappeared and the blood has reached a more normal condition. Again farinaceous or even light diet in hospital is somewhat monotonous, and it was often extremely difficult to get patients to take sufficient. It is also difficult to get the average hospital patient to realise the importance of such a restricted diet, and many continually grumble about the diet. The disadvantages of the light

diet are thus very real, but the results seem to justify one in enforcing such treatment. Humphry reports improvement in three cases treated by open air method and this method appears to be very beneficial especially during convalesence. The other most important point in regard to the treatment is rest. In all severe cases the patient ought to be kept at rest in bed till the symptoms abate and the temperature shows no evening pyrexia. One must be guided by the general condition of the patient as to whether or not he may be allowed to go about, but the important question especially in working men comes to be answered when they have sufficently recovered to be able to leave hospital. Hard work seems inevitably to predispose to a relapse, hence once a patient has been diagnosed to have pernicious anaemia it is important that he should have no hard manual labour to perform, and he should be told to regulate his life very much in the same way as a patient with valvular cardiac disease is told to do.

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